

Hypertension in adults: diagnosis and management

[D] Evidence review for targets

NICE guideline NG136

*Intervention evidence review underpinning recommendations
1.4.16 and 1.4.20 to 1.4.22 in the guideline*

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*This evidence review was developed by
the National Guideline Centre*

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1 Targets

1.1 Review question: Should targets used for antihypertensive therapy be based on blood pressure, cardiovascular risk or a combination of both?

1.2 Introduction

In individuals diagnosed with hypertension, the current treatment approach is to lower blood pressure to a target value to reduce their risk of future cardiovascular events. An alternative approach would be to target a reduction in cardiovascular risk directly, rather than aim for a blood pressure target. It is foreseeable that this might be achieved through a combination of antihypertensive therapy, lifestyle changes, lipids-lowering medication and other medications that act on the cardiovascular system. The potential advantage of this alternative approach is that it might remove the necessity for regular blood pressure monitoring with an associated time and cost savings for both the person with hypertension and healthcare providers. This chapter reviews the evidence of whether targets for antihypertensive therapy should be based on blood pressure, cardiovascular risk or a combination of both.

1.3 PICO table

For full details, see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Population: Adults (over 18 years) with primary hypertension Stratify by: presence or absence of type 2 diabetes
Intervention(s)	Blood pressure targets Cardiovascular risk targets Combination of blood pressure target and cardiovascular risk target
Comparison(s)	<ul style="list-style-type: none"> • Types of targets compared to each other • Blood pressure and cardiovascular risk targets combined compared to either target type alone • No target
Outcomes	<p>Critical</p> <ul style="list-style-type: none"> • All-cause mortality • Health-related quality of life • Stroke (ischaemic or haemorrhagic) • Myocardial infarction (MI) <p>Important</p> <ul style="list-style-type: none"> • Heart failure needing hospitalisation • Vascular procedures (including lower limb, coronary and carotid artery procedures) • Angina needing hospitalisation • Discontinuation or dose reduction due to side effects • Resource use • Side effect 1: Acute kidney injury • Side effect 2: New onset diabetes • Side effect 3: Change in creatinine or estimated glomerular filtration rate (eGFR)

	<ul style="list-style-type: none">• Side effect 4: Hypotension (dizziness)• [Combined cardiovascular disease outcomes in the absence of MI and stroke data]• [Coronary heart disease outcome in the absence of MI data]
Study design	Randomised control trials (RCT) and systematic reviews (SR)

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.⁸¹ Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

1.5 Clinical evidence

1.5.1 Included studies

No relevant clinical studies comparing different types of targets were identified.

See also the study selection flow chart in appendix C.

1.5.2 Excluded studies

See the excluded studies list in appendix I.

1.5.3 Summary of clinical studies included in the evidence review

No relevant clinical studies were identified.

1.5.4 Quality assessment of clinical studies included in the evidence review

No relevant clinical studies were identified.

1.6 Economic evidence

1.6.1 Included studies

No relevant health economic studies were identified.

1.6.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.6.3 Resource costs

See section 2.6.3.

1.7 Evidence statements

1.7.1 Clinical evidence statements

No relevant published evidence was identified.

1.7.2 Health economic evidence statements

No relevant economic evaluations were identified.

2 Blood pressure targets

2.1 Review question: What is the optimum blood pressure target for adults with treated primary hypertension?

2.2 Introduction

The risks associated with hypertension continue to increase as blood pressure rises. Therefore, when an individual is diagnosed with hypertension, the current aim of treatment (pharmacological or otherwise) is to reduce blood pressure to a lower level, thus reducing the risk of future cardiovascular events. This lower blood pressure level (or target) is selected based on the benefit of reducing future cardiovascular events but balanced against the risk associated with having a blood pressure that is too low.

Since the last guideline was published in 2011, there have been multiple randomised controlled trials (RCT) that have investigated whether the blood pressure target should be lower than that which is currently set (generally less than 140/90 mmHg depending on comorbidities). These studies have resulted in significant debate within the medical community as to what the optimum blood pressure target should be. This chapter reviews the evidence from these and other studies to try to identify the optimum blood pressure target.

2.3 PICO table

For full details, see the review protocol in appendix A.

Table 2: PICO characteristics of review question

Population	Population: Adults (over 18 years) with primary hypertension <ul style="list-style-type: none"> • Stratify by: presence or absence of type 2 diabetes
Intervention(s)	Blood pressure or cardiovascular risk targets <ul style="list-style-type: none"> • Systolic blood pressure targets: <ul style="list-style-type: none"> ○ Below 120 mmHg ○ 120–129 mmHg ○ 130–139 mmHg ○ 140–59 mmHg ○ 160 mmHg or higher • Diastolic blood pressure targets: <ul style="list-style-type: none"> ○ Below 80 mmHg ○ 80–84 mmHg ○ 85–89 mmHg ○ 90–94 mmHg ○ 95 mmHg or higher
Comparison	Compared to each other
Outcomes	Critical <ul style="list-style-type: none"> • All-cause mortality • Health-related quality of life • Stroke (ischaemic or haemorrhagic) • Myocardial infarction (MI) Important <ul style="list-style-type: none"> • Heart failure needing hospitalisation • Vascular procedures (including lower limb, coronary and carotid artery procedures)

	<ul style="list-style-type: none">• Angina needing hospitalisation• Discontinuation or dose reduction due to side effects• Resource use• Side effect 1: Acute kidney injury• Side effect 2: New onset diabetes• Side effect 3: Change in creatinine or eGFR• Side effect 4: Hypotension (dizziness)• [Combined cardiovascular disease outcomes in the absence of MI and stroke data]• [Coronary heart disease outcome in the absence of MI data]
Study design	RCTs, systematic reviews (SR)

2.4 Methods and process

This evidence review was developed using the methods and processes described in Developing NICE guidelines: the manual.⁸¹ Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

2.5 Clinical evidence

2.5.1 Included studies

When setting the protocol for this review question, the committee agreed a priori that in the absence of evidence informing whether blood pressure or cardiovascular risk should be used, this question would focus on blood pressure targets, which is current clinical practice.

Three studies were included in the review; these are summarised in Table 3 below.^{1, 2, 20, 31, 84, 95, 116, 123} Evidence from these studies is summarised in the clinical evidence summary below (Table 4). These studies compared the following:

- Systolic blood pressure of below 120 mmHg versus below 140 mmHg (2 studies)
- Systolic blood pressure of below 130 mmHg versus below 140 mmHg (1 study)

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

2.5.2 Excluded studies

Four Cochrane reviews relevant to this review question were identified. Garrison 2017⁴⁶ was excluded because the population included people with established cardiovascular disease and crossover trials were included. Arguedas 2009⁶ and Arguedas 2013⁵ were excluded due to including people with various chronic renal conditions or previous cardiovascular disease, who were excluded from this review protocol.

See the excluded studies list in appendix I. Table 22 outlines the full excluded studies list, and Table 21 provides additional detail of studies that were included in the previous guideline iteration (CG127) but excluded from this update.

2.5.3 Summary of clinical studies included in the evidence review

Table 3: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
ACCORD study group, 2010¹	(n=1,558) Intervention 1: Systolic blood pressure (BP) targets <120 mmHg (n=1,582) Intervention 2: Systolic BP targets <140 mmHg	Primary hypertension and type 2 diabetes (subgroup analysis of those without previous cardiovascular disease (CVD); n=3,140). Aged 40 years and older (mean 62.2 years) Systolic BP between 130 and 180 mmHg (mean 153.3/89.8 mmHg)	At 4.7 years: <ul style="list-style-type: none"> • Composite outcome of stroke (non-fatal), MI (non-fatal), and CVD (fatal) 	Participants also randomised to either intensive or standard glycaemic control in a 2x2 factorial design. BP measured using an automated device (Omron 907) after 5 minutes rest with the participant seated in a chair (average of 3 measurements).
SPRINT Study Group 2015 (Wright 2015¹²³, Ambrosius 2014^{2, 20, 31, 84, 95})	(n=3,348) Intervention 1: Systolic BP targets <120mmHg (n=3,367) Intervention 2: Systolic BP targets <140 mmHg	Primary hypertension without type 2 diabetes (subgroup analysis of those without chronic kidney disease [CKD]; n=6,715) Mean age 66.3 years. 22% of participants were above the age of 74 14% had clinical CVD 61% had Framingham risk score above 15% (mean 23.9) Mean standard deviation (SD) baseline BP 139.9/79.5 (15.4/11.5) mmHg (Systolic	At 3.26 years: <ul style="list-style-type: none"> • All-cause mortality • Stroke • MI • Heart failure • Resource use (mean reduction in Systolic BP, mean number of pills) • Acute kidney injury (defined by creatinine) • >30% reduction in eGFR • Hypotension • Orthostatic hypotension with and without dizziness • Syncope • Injurious falls 	Titration of medications to target is based on a mean of 3 office blood pressure measurements obtained in the seated position using an automated measurement device (Omron Healthcare, Lake Forest, IL, USA). Actual strategy for blood pressure measurement varied within SPRINT. The majority of participants (n=4,082) were alone throughout measurement. 2,247 participants were never alone, 1,746 were alone for the rest period only, and 570 were alone for BP measurement only (Note that these numbers include the

Study	Intervention and comparison	Population	Outcomes	Comments
		BP range 130–180 mmHg)	<ul style="list-style-type: none"> Resource use (mean BP) 	<p>CKD population).</p> <p>Downgraded for indirectness due to methods of measuring blood pressure</p>
Cardio-SIS, Verdecchia 2009 ¹¹⁶	(n=558) Intervention 1: Systolic BP targets <130 mmHg (n=553) Intervention 2: Systolic BP targets <140 mmHg	<p>Primary hypertension without type 2 diabetes (n=1,111)</p> <p>Aged 55 years and older (mean 67 [7] years)</p> <p>Systolic BP of 150 mmHg or over</p>	<p>At 2 years:</p> <ul style="list-style-type: none"> All-cause mortality Stroke MI Heart failure requiring hospitalisation Resource use (mean BP reduction, mean number of pills) Dizziness 	<p>Participants were taking antihypertensive treatment for at least 12 weeks and had 1 additional risk factor as described in the guidelines of European Society of Hypertension (ESH)</p> <p>BP measured with standard mercury sphygmomanometers, after people had been seated for at least 10 minutes. BP was the average of 3 consecutive readings at every visit</p>

See appendix D for full evidence tables.

2.5.4 Quality assessment of clinical studies included in the evidence review

Table 4: Clinical evidence summary: Below 120 mmHg versus below 140 mmHg (non-diabetic population)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with 120 mmHg versus 140 mmHg (95% CI)
All-cause mortality	6,715 (1 study) 3.26 years	LOW ^{1,2} due to imprecision, indirectness	RR 0.74 (0.56 to 0.98)	34 per 1,000	9 fewer per 1,000 (from 1 fewer to 15 fewer)
Stroke	6,715 (1 study)	VERY LOW ^{1,2} due to imprecision,	RR 0.82 (0.53 to	13 per 1,000	2 fewer per 1,000 (from 6 fewer to 4 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with 120 mmHg versus 140 mmHg (95% CI)
	3.26 years	indirectness	1.28)		
MI	6,715 (1 study) 3.26 years	LOW ^{1,2} due to imprecision, indirectness	RR 0.75 (0.53 to 1.07)	21 per 1,000	5 fewer per 1,000 (from 10 fewer to 1 more)
Heart failure	6,715 (1 study) 3.26 years	MODERATE ² due to indirectness	RR 0.44 (0.26 to 0.73)	14 per 1,000	8 fewer per 1,000 (from 4 fewer to 11 fewer)
Acute kidney injury (KDIGO modified criteria based on serum creatinine concentration only; stages 1, 2 and 3)	6,715 (1 study) 3.26 years	MODERATE ² due to indirectness	RR 2.17 (1.48 to 3.18)	11 per 1,000	13 more per 1,000 (from 5 more to 25 more)
More than 30% reduction in eGFR	6,715 (1 study) 3.26 years	MODERATE ² due to indirectness	RR 3.52 (2.49 to 4.99)	12 per 1,000	30 more per 1,000 (from 18 more to 47 more)
Hypotension (serious adverse event)	6,693 (1 study) 3.26 years	MODERATE ² due to indirectness	RR 2.11 (1.35 to 3.29)	8 per 1,000	9 more per 1,000 (from 3 more to 19 more)
Orthostatic hypotension (with dizziness); 20 mmHg drop in systolic or a10 mmHg drop in diastolic BP at 1 minute after standing	6,693 (1) 3.26 years	LOW ^{1,2} due to imprecision, indirectness	RR 0.79 (0.52 to 1.21)	14 per 1,000	3 fewer per 1,000 (from 7 fewer to 3 more)
Orthostatic hypotension (without dizziness); 20 mmHg drop is systolic of 10 mmHg drop in diastolic BP at 1 minute after standing	6,693 (1) 3.26 years	LOW ^{1,2} due to imprecision, indirectness	RR 0.86 (0.77 to 0.96)	166 per 1,000	23 fewer per 1,000 (from 7 fewer to 38 fewer)
Syncope (serious adverse event or emergency	6,693 (1)	LOW ^{1,2} due to imprecision,	RR 1.53 (1.14 to	21 per 1,000	11 more per 1,000 (from 3 more to 22 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with 120 mmHg versus 140 mmHg (95% CI)
department visit)	3.26 years	indirectness	2.06)		
Injurious falls, defined as a fall that resulted in evaluation in an emergency department or that resulted in hospitalisation	6,693 (1 study) 3.26 years	LOW ^{1,2} due to imprecision, indirectness	RR 1.24 (0.93 to 1.64)	25 per 1,000	6 more per 1,000 (from 2 fewer to 16 more)
Mean systolic BP	6,715 (1 study) 6 months	LOW ² due to indirectness		Control group mean not reported	The mean blood pressure was 15mmHg lower in the intervention group (14.7 lower to 15.4 lower)
Mean number of medications	6,715 (1 study) 3.26 years	LOW ² due to indirectness		Mean number of medications in the control group was 1.8	The mean number of medications in the intervention groups was 1 higher (0.94 to 1.06 higher)

¹ Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
² The majority of the evidence included an indirect outcome or intervention (downgrade by 1 increment) or a very indirect outcome or intervention (downgrade by 2 increments)

Table 5: Clinical evidence summary: Below 120 mmHg versus below 140 mmHg (diabetic population)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with 120 mmHg versus 140 mmHg (diabetic population; 95% CI)
Cardiovascular events: Stroke (non-fatal), MI (non-fatal), CVD (fatal)	3,140 (1 study) 4.7 years	LOW ¹ due to imprecision	RR 0.93 (0.52 to 1.67)	15 per 1,000	1 fewer per 1,000 (from 7 fewer to 10 more)

¹ Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 6: Clinical evidence summary: Below 130 mmHg versus below 140 mmHg (non-diabetic population)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with <130 mmHg versus <140 mmHg (non-diabetic population; 95% CI)
All-cause mortality	1,111 (1 study) 2 years	LOW ¹ due to imprecision	RR 0.79 (0.21 to 2.94)	9 per 1,000	2 fewer per 1,000 (from 7 fewer to 18 more)
Stroke	1,141 (1 study) 2 years	LOW ¹ due to imprecision	RR 0.46 (0.14 to 1.5)	15 per 1,000	8 fewer per 1,000 (from 13 fewer to 8 more)
MI	1,111 (1 study) 2 years	LOW ¹ due to imprecision	RR 0.66 (0.19 to 2.33)	11 per 1,000	4 fewer per 1,000 (from 9 fewer to 14 more)
Heart failure admission	1,111 (1 study) 2 years	LOW ¹ due to imprecision	RR 0.42 (0.11 to 1.63)	13 per 1,000	7 fewer per 1,000 (from 11 fewer to 8 more)
Dizziness (hypotension)	1,111 (1 study) 2 years	VERY LOW ^{1,2,3} due to risk of bias, indirectness, imprecision	RR 0.5 (0.09 to 2.69)	7 per 1,000	4 fewer per 1,000 (from 7 fewer to 12 more)
Mean reduction in systolic BP (mmHg)	1,111 (1 study) 2 years	MODERATE ¹ due to imprecision		The mean reduction in systolic blood pressure in the control group was -23.5	The mean reduction in blood pressure in the intervention groups was 3.8 lower (5.07 to 2.53 lower)

¹ Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

² Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

³ The majority of the evidence included an indirect outcome (downgrade by 1 increment) or a very indirect outcome (downgrade by 2 increments)

See appendix F for full GRADE tables.

2.6 Economic evidence

2.6.1 Included studies

No relevant health economic studies were identified.

2.6.2 Excluded studies

Three economic studies relating to this review question were identified but were excluded due to limited applicability.^{34, 62, 91} These are listed in appendix I, with the reasons for exclusion.

See also the health economic study selection flow chart in appendix G.

2.6.3 Resource costs

Lower blood pressure targets tend to be associated with more intensive treatment, which creates a resource difference in terms of both drugs and monitoring as well as potential adverse events. However, a lower blood pressure is also generally associated with lower cardiovascular events which would be associated with cost savings.

2.7 Evidence statements

2.7.1 Clinical evidence statements

Below 120 mmHg versus 140 mmHg (non-diabetic population)

Low quality evidence from 1 study with a total of 6,715 participants showed a clinically important benefit of a target of below 120 mmHg compared to 140 mmHg for all-cause mortality and MI at 3.26 years. Moderate quality evidence from this study showed a clinically important benefit of below 120 mmHg for heart failure at 3.26 years but an increased incidence of acute kidney injury, greater reduction in eGFR and increased occurrence of hypotension.

Low quality evidence from the same study did not demonstrate a difference between targets for occurrence of stroke or orthostatic hypotension. However, there was an clinically important increase in incidence of syncope and injurious falls with a target of below 120 mmHg but a greater reduction in blood pressure at 3.26 years (low quality evidence).

Below 120 mmHg versus 140 mmHg (diabetic population)

Low quality evidence from 1 study with a total of 3,140 participants showed no clinically important difference between targets for occurrence of major cardiovascular events at 4.7 years.

Below 130 mmHg versus 140 mmHg (non-diabetic population)

Low quality evidence from 1 study with a total of 1,111 participants showed a clinically important benefit for a target of below 130 mmHg in terms of all-cause mortality, stroke and heart failure admissions at 2 years and showed no clinically important difference for MI at 2 years. However, evidence from the same study did not demonstrate a difference between targets for dizziness (very low quality evidence) or mean reduction in blood pressure (moderate quality evidence).

2.7.2 Health economic evidence statements

No relevant economic evaluations were identified.

2.8 The committee's discussion of the evidence

2.8.1 Interpreting the evidence

2.8.1.1 The outcomes that matter most

The committee considered all-cause mortality, quality of life, stroke and myocardial infarction to be critical outcomes for decision-making. Heart failure, angina, vascular procedures, adverse events and resource use were also considered important outcomes for decision-making. These outcomes and prioritisation were applied for both review questions, however no evidence was identified for any outcome for the question informing whether cardiovascular risk or blood pressure targets should be used.

For the second question focussing on the most appropriate blood pressure target in the population without type 2 diabetes, evidence was identified for all outcomes other than angina and vascular procedures. In the type 2 diabetes population, the only evidence identified was an indirect outcome of major cardiovascular events.

2.8.1.2 The quality of the evidence

No evidence was identified for the first question.

For the question informing the most appropriate blood pressure target the evidence ranged from very low to moderate quality due mainly to imprecision and indirectness. The committee agreed that the majority of evidence was indirect due to issues related to the population and intervention, and this was consequently difficult to interpret. One of the reasons for intervention indirectness was related to 1 study measuring blood pressure using an automated technique set on a delay, which is not current standard practice in the UK. The committee agreed that blood pressure values using these methods could be lower than those determined using methods common in UK clinical practice and would be impractical to implement in a UK setting. As a result, some of the evidence for blood pressure targets could not be easily translated to recommendations.

2.8.1.3 Benefits and harms

Due to the lack of any relevant evidence comparing the use of blood pressure targets and cardiovascular risk based targets, the committee agreed to follow their a-priori decision if this scenario occurred that the evidence review should focus on blood pressure targets. It was agreed that as aiming for a target blood pressure when managing hypertension was current clinical practice and with an absence of evidence it would be inappropriate to change practice to aiming specifically for a lower cardiovascular risk. This was agreed as the most appropriate decision both in terms of feasibility in clinical practice, but also for people with hypertension who would be more familiar with monitoring their blood pressure in this way.

Hypertension without type 2 diabetes

The committee discussed the evidence for blood pressure targets in people with hypertension without type 2 diabetes, for which 2 studies were identified. The committee discussed a large trial conducted in the US, which compared clinic systolic blood pressure targets of 120 mmHg to 140 mmHg. The committee raised substantial concerns about the methodology used within the trial and agreed that the evidence did not reflect current methods of measuring blood pressure in a UK setting. As a result, the committee agreed that this evidence was insufficient to change the currently recommended blood pressure target.

One of the committee's main concerns was related to the use of an automated blood pressure device set on a time delay in the trial, which is not current standard practice within the UK and does not translate easily to the blood pressure values or targets generated from methods used in the UK. In this trial, staff set a measurement delay of 5 minutes and then blood pressure measurements were taken after this time. During the procedure, staff could leave the room, and the average of the readings could be used as the blood pressure measurement. The committee noted that this differs from automated measurements where the healthcare professional would remain in the room while the blood pressure measurements were being taken. The committee agreed that automated devices used with a rest period without the healthcare professional in the room could give lower values than the methods used for similar devices in day-to-day UK clinical practice, with some evidence suggesting the difference could be as much as 13 mmHg. The committee agreed that this was another factor that resulted in less generalisable evidence because a systolic blood pressure target of 120 mmHg or 140 mmHg within this evidence could not be directly translated to the same target within UK practice. These differences in practice therefore cast doubt on the treatment effect reported, and the committee could not infer how these methods and results could be translated to current UK practice.

The committee discussed the practicality of implementing an automated measurement technique in the UK and discussed whether it would be feasible due to the resource impact this would have in providing the devices; most clinical practice settings would have to adapt

current practices to meet the requirements of automated measurement (for example, allocating more staff time for blood pressure measurement and providing rooms for the quiet resting period required). Although the committee noted that some specialist services might already use automated devices in this way, this is likely to be a very small number of less than 1% of services.

The treat-to-target protocol used in the evidence down-titrated participants' medication if their blood pressure fell below the pre-specified target. For example, in the standard treatment group (<140 mmHg systolic target), medications were reduced if participants' systolic blood pressure fell below 130 mmHg on a single visit or less than 135 mmHg on 2 consecutive visits. The committee had concerns that this method significantly contrasted UK current practice, as most healthcare professionals would not reduce medication after a target had been reached unless people became symptomatic with a low blood pressure. The committee also noted that the most common drug taken away in this study was diuretics, and the number of participants taking thiazide diuretics at follow-up differed between the 2 intervention arms of the study. The committee noted that this could have biased the heart failure outcome identified in this review because diuretics are known to improve the symptoms of heart failure.

The committee had considerable concerns about the applicability of the population in the evidence: the population had a mean systolic blood pressure of 139/90 mmHg at baseline, which would be defined as well controlled based on current definitions in UK, particularly as a third of participants had a systolic blood pressure of less than 132 mmHg at baseline. Although it was unclear how many participants were 'down-titrated', the committee noted that participants in the 140 mmHg target group may not have required any additional treatment, or could have been 'down-titrated'.

The population also had a high cardiovascular risk, with a Framingham cardiovascular risk score of 15% on treatment. The committee agreed it was difficult to infer what the benefit of a lower target might be in a population with a lower risk than this. Over 90% of the population were taking between 1–3 antihypertensive treatments at baseline, which means the actual untreated baseline blood pressure was not known, leading to further difficulties in translating this evidence to recommendations. The committee discussed the age of participants within the evidence and agreed that this evidence was less generalisable to older or frailer people with hypertension. The mean age of participants in the evidence was 66.3 years, and 22% of participants were above the age of 74. The study also excluded residents in nursing homes. Although the criteria state that residence in an assisted living facility (approximately equivalent to residential care in the UK) was not an exclusion, no assisted living residents were enrolled. Also, people thought to have a prognosis of less than 3 years were excluded, as were those with dementia and those with 'any factors judged by the clinical team to be likely to limit adherence to interventions'. The committee agreed to retain recommendations for a target of 150/90 mmHg in this older population.

Despite the limited applicability of the evidence, the committee agreed that the evidence showed a benefit of a lower target for mortality, myocardial infarction and heart failure. However, the evidence also showed moderate harms of the lower target in terms of acute kidney injury, hypotension and injurious falls and no clinically important difference for stroke. The committee discussed this benefit and harms trade off and agreed that to some extent the harms of the lower target could outweigh the benefits, although further evidence was needed to identify the longer-term implications of the adverse events associated with lower blood pressure targets. The committee noted that the injurious falls outcome was defined as severe falls resulting in hospitalisation and agreed that this was an important outcome to consider, particularly in terms of the implications this could have for elderly populations. The committee also agreed that the increased risk of acute kidney injury highlighted in this review could be detrimental to people's health. However, the committee noted that a longer follow-up time was needed to understand the full implications of this outcome; it was unclear whether this effect would be maintained in the long term or improve or worsen over time, with participants

followed up for a median time of 3.26 years. There was concern that the large US trial included within this evidence was discontinued early, which means that longer-term implications, both positive and negative, was not known.

The committee also discussed evidence comparing systolic blood pressure targets of 140 mmHg to 130 mmHg. The evidence was low quality, from 1 relatively small study, and the committee agreed that although this suggested a benefit of lower treatment targets, it was insufficient to make a new recommendation. The evidence showed a clinically important benefit for mortality, stroke and heart failure admissions. There was no clinically important difference for myocardial infarction, dizziness, and blood pressure difference. Other key factors that the committee took into account were that participants were treated at baseline, thus making it difficult to determine how these blood pressure targets related to a newly diagnosed untreated population. The committee also noted that evidence for adverse events was limited only to dizziness. The committee agreed that other adverse event outcomes such as acute kidney injury were particularly important outcomes for decision-making for this question.

Hypertension with type 2 diabetes

The evidence for different blood pressure targets for people with type 2 diabetes was limited. The review identified a subgroup analysis of a large trial in participants who did not have previous cardiovascular events. There was no clinically important difference for major cardiovascular events between clinic systolic blood pressure targets of 120 mmHg compared to 140 mmHg. The committee had considerable concerns about the applicability of the population within the evidence. Some participants had a baseline systolic blood pressure below 140 mmHg, which would be defined as well controlled in UK current practice. The committee agreed that the evidence was flawed, and therefore made interpretation of the results difficult. The results suggested no benefit of lowering the blood pressure target for people with type 2 diabetes although there was no evidence for most of the individual outcomes sought in this review. The committee were unsure why there would not be a benefit of treatment in this population compared to the possible benefit of treatment seen in the population without type 2 diabetes; therefore, the committee agreed that there was not enough evidence to inform recommendations. The committee discussed the previous targets of 140/80 mmHg in the type 2 diabetes guideline (NG28), which were based on consensus. It agreed there was not enough evidence related to lower diastolic blood pressure to retain this recommendation and that the target should be the same for people irrespective of presence of type 2 diabetes.

The previous recommendations for people with type 2 diabetes (in NICE's guideline on type 2 diabetes) also suggested a blood pressure target below 130/80 mmHg in the presence of kidney, cerebrovascular or eye disease. The committee noted that the evidence behind this recommendation was based on 2 small studies in people without hypertension. Furthermore, these 2 studies were not designed to measure the benefit of treatment in people who already had target organ damage, but rather the studies predominantly assessed the incidence of target organ damage based on a target diastolic blood pressure. The committee therefore agreed that there was insufficient evidence to recommend a different blood pressure target for this subgroup. They noted that people post-stroke and with later-stage chronic kidney disease are covered by other NICE guidelines.

Summary

Taking the evidence into account as a whole, along with the substantial limitations of the evidence, the committee agreed that it couldn't recommend a lower blood pressure target than currently recommended. The committee agreed that the harms of treatment and limitations of the evidence, particularly in terms of indirectness and lack of applicability, could not be ignored. It therefore agreed that the evidence could not inform altering the existing

recommendations, as there was limited information to assess fully whether there is a benefit of a lower target and if this outweighs the associated harms.

2.8.2 Cost effectiveness and resource use

Three economic studies relating to this review were identified but excluded due to limited applicability.

Lower blood pressure targets tend to be associated with more intensive treatment, which creates a resource difference in terms of both drugs and monitoring as well as potential adverse events. However, a lower blood pressure is also generally associated with lower cardiovascular events. If a low target strategy leads to fewer events, then this is likely to lead to a higher quality of life for an average cohort than a standard target strategy, as there would be fewer people dying and fewer people having events. The cost effectiveness of a lower target depends on whether the QALY gain of the lower target intervention compared to that of a standard target intervention is large enough to justify any additional cost of the more intensive strategy.

The clinical review showed that there are differences in resource use between a low and high target strategy in terms of needing on average 1 more drug in the low target group. This led to more adverse events, but lower blood pressure and less mortality and cardiovascular events for some outcomes.

The committee's discussion focused around the SPRINT study and its methodological flaws, as that was a debate necessary in order to decide if the outcomes of the study were felt to be valid. The overall conclusion was that there are many limitations to SPRINT such as how it does not match the population on the guideline review clinical protocol, as we are talking about newly diagnosed people; the participants were considered high risk; and the measurement method in the SPRINT study was not considered appropriate. The concerns about how to translate the targets and blood pressures in the trial to clinical practice because of the population being on treatment already, for example, was also problematic in trying to equate those values in the SPRINT trial to values in a recommendation.

The middle ground decided upon was that the target currently in the recommendation from the previous guideline of 140/90 mmHg should be a consistent target. The committee wanted to emphasise that a target of 140/90 mmHg is a target that should be achieved (in other words, the blood pressure should be below this level) and maintained when the person is subsequently monitored (which should be annual according to the guideline). It was mentioned that in practice it takes around 1.9 tablets to get to a target of 140 mmHg systolic blood pressure. At the moment, the current target is not achieved in approximately 50% of people, so a more rigorous approach to making sure the target is met is likely to mean more resource use is required in terms of medication and follow-up or monitoring. This may have a knock-on effect of more adverse events but also a reduction in cardiovascular events. Evidence from other reviews in this guideline have shown that antihypertensive treatment is effective (review 3.1), and the cost effectiveness of antihypertensives is well established (as shown through the first line drugs model in the 2011 version of this guideline). Therefore, although the clinical evidence was not felt strong enough, for the reasons described above, to lower the target, the committee felt strongly that it should be reinforced that the target previously recommended should be met with more robustness in practice. This is likely to be a cost effective use of resources due to the events avoided and quality of life gained through stricter control of the target.

The recommendations have remained split by age over and under 80. The target for people aged over 80 (150/90 mmHg) was informed mainly by evidence from the HYVET study, which was identified in the previous guideline (CG127). This study was not included within this evidence review because it compared a blood pressure target to placebo treatment, rather than comparing different blood pressure targets to each other. The committee agreed

that there was no new evidence to challenge this recommendation, and that there is a lack of data specifically on people aged over 80. Therefore, the recommendations have been carried forward, with the reinforcement of maintaining blood pressure consistently below the target; however, a research recommendation has been drafted in order to inform future guidance.

In people with type 2 diabetes, the previous recommendations in NG28⁸² had a target of 140/80 mmHg. The clinical evidence identified in this review for this population compared a target of systolic blood pressure of 140 mmHg to 120 mmHg. The committee felt this did not support that the target should be lowered for those with hypertension and type 2 diabetes beyond a stricter recommendation to maintain blood pressure below 140 mmHg. The committee discussed how this would be a slight difference to the previous recommendation in the type 2 diabetes guideline due to the diastolic blood pressure target difference. This might lead to less treatment as the diastolic target is slightly higher (that is, moving from 140/80 mmHg to 140/90 mmHg for people with type 2 diabetes); however, generally it is the systolic target that is followed. The recommendations in the diabetes guideline on a lower target (below 130/80 mmHg) for those with kidney, eye or cerebrovascular damage were discussed, and the committee's opinion on the evidence that informed that recommendation was that it was not in the right population. There was no evidence for this population identified in this guideline because this guideline is not covering the comorbidities populations referred to. The committee felt that this recommendation did not need to be carried forward because it was not based on strong evidence. Some of these comorbid populations covered as part of the diabetes guideline would already be covered in other guidelines e.g. those with hypertension, diabetes and CKD should follow the targets in the CKD guideline (⁸⁰). Therefore the population with hypertension and diabetes referred to here are those with no major renal impairment.

Additionally, some new recommendations were made to ensure measurement of blood pressure is happening properly. Measuring postural blood pressure could mean that less treatment is needed if the postural blood pressure is assessed against the target, which tends to be lower, rather than the sitting blood pressure.

Overall, the recommendations are likely to lead to tighter target control in a hypertensive population, as current practice doesn't always maintain the target recommended in the previous guideline. This is likely to have a resource impact in terms of additional monitoring and treatment required to get those to the target that are not currently meeting the target, given that there may be a large proportion of people with uncontrolled hypertension according to the health survey for England. For those with diabetes without co-morbidities, the diabetes guideline also had stricter wording in terms of people needing to meet 'consistently' the recommended targets, hence that population is already likely to be more well controlled. Those with diabetes and co-morbidities that are not covered by other guidelines, now have slightly more flexibility in their (new) blood pressure target, which is likely similar to previously attained levels. This may mean less treatment, monitoring and fewer adverse events in some cases, but the majority of people with hypertension and diabetes are also likely to have target organ damage for example, albuminuria and therefore would be either be maintained on current treatment or their initiation on treatment will be covered in other guidance.

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Appendices

Appendix A: Review protocols

Table 7: Review protocol: targets

Field	Content
Review question	Should targets used for antihypertensive therapy be based on blood pressure, cardiovascular risk or a combination of both?
Type of review question	Intervention review A review of health economic evidence related to the same review question was conducted in parallel with this review. For details, see the health economic review protocol for this NICE guideline.
Objective of the review	To establish whether blood pressure or cardiovascular risk targets improve outcomes more for adults with hypertension
Eligibility criteria – population / disease / condition / issue / domain	Population: Adults (over 18 years) with primary hypertension
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	The following types of targets used to inform antihypertensive therapy*: <ul style="list-style-type: none"> • Blood pressure targets, including systolic, diastolic or a combination of both. • Cardiovascular risk targets, such as: <ul style="list-style-type: none"> ◦ QRISK2 • Blood pressure and cardiovascular risk targets combined <p>*Note that treatment must be received for a minimum of 1 year</p>
Eligibility criteria – comparator(s) / control or reference (gold) standard	<ul style="list-style-type: none"> • Types of targets compared to each other • Blood pressure and cardiovascular risk targets combined compared to either target type alone • No target
Outcomes and prioritisation	All outcomes to be measured at a minimum of 12 months. Where multiple time points are reported within each study, the longest time point only will be extracted. <p>Critical</p> <ul style="list-style-type: none"> • All-cause mortality • Health-related quality of life • Stroke (ischaemic or haemorrhagic) • MI <p>Important</p> <ul style="list-style-type: none"> • Heart failure needing hospitalisation • Vascular procedures (including lower limb, coronary and carotid artery procedures) • Angina needing hospitalisation • Discontinuation or dose reduction due to side effects • Resource use • Side effect 1: Acute kidney injury • Side effect 2: New onset diabetes • Side effect 3: Change in creatinine or eGFR • Side effect 4: Hypotension (dizziness)

	<ul style="list-style-type: none"> • [Combined cardiovascular disease outcomes in the absence of MI and stroke data] • [Coronary heart disease outcome in the absence of MI data]
Eligibility criteria – study design	RCTs and SRs
Other inclusion exclusion criteria	<p>Exclusions:</p> <ul style="list-style-type: none"> • Studies including participants with type 1 diabetes or chronic kidney disease (A3 [heavy proteinuria]) or A2 or above for participants with type 2 diabetes. • Indirect populations with secondary causes of hypertension such as tumours or structural vascular defects (Conn’s adenoma, pheochromocytoma, renovascular hypertension) • Pregnant women • Children (under 18 years)
Proposed sensitivity / subgroup analysis, or meta-regression	<p>Subgroups for analysis of heterogeneity:</p> <ul style="list-style-type: none"> • Age (under 55, 55–75, over 75)* • Severity (moderate [140–159/90–99 mmHg] versus severe [160/100 mmHg or higher]) • Family origin (African and Caribbean, White, South Asian) <p>*To note that evidence in those over 80 years if this evidence will also be analysed as a separate subgroup when reported separately.</p>
Selection process – duplicate screening / selection / analysis	A senior research fellow will undertake quality assurance prior to completion.
Data management (software)	<p>Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5).</p> <p>GRADEpro was used to assess the quality of evidence for each outcome.</p> <p>Endnote for bibliography, citations, sifting and reference management.</p>
Information sources – databases and dates	<p>Medline, Embase, the Cochrane Library</p> <p>Language: Restrict to English only</p> <p>Date cut off: from 2000</p> <p>Key papers:</p> <p>Cochrane review (2017): http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010316.pub2/full</p>
Identify if an update	Yes, 2011
Author contacts	https://www.nice.org.uk/guidance/cg127
Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for 1 database	For details, please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details, please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	<p>Standard study checklists were used to appraise individual studies critically. For details please see section 6.2 of Developing NICE guidelines: the manual</p> <p>The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the ‘Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox’</p>

	developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details, please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details, please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details, please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details, please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details, please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Anthony Wierzbicki in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details, please see Developing NICE guidelines: the manual.
Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds the NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 8: Review protocol: blood pressure targets

Field	Content
Review question	What is the optimum blood pressure or cardiovascular risk target for adults with treated primary hypertension?
Type of review question	Intervention review A review of health economic evidence related to the same review question was conducted in parallel with this review. For details, see the health economic review protocol for this NICE guideline.
Objective of the review	To establish which blood pressure or cardiovascular disease risk target should be aimed for* *In the absence of evidence comparing blood pressure versus cardiovascular targets (review 3.2), this review will focus on blood pressure targets.
Eligibility criteria – population / disease / condition / issue / domain	Population: Adults (over 18 years) with primary hypertension Stratify by: <ul style="list-style-type: none"> • Presence or absence of type 2 diabetes
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Blood pressure/cardiovascular risk targets* <ul style="list-style-type: none"> • Systolic blood pressure targets: <ul style="list-style-type: none"> ○ Below 120 mmHg ○ 120–129 mmHg

	<ul style="list-style-type: none"> ○ 130–139 mmHg ○ 140–59 mmHg ○ 160 mmHg or higher ● Diastolic blood pressure targets: <ul style="list-style-type: none"> ○ Below 80 mmHg ○ 80–84 mmHg ○ 85–89 mmHg ○ 90–94 mmHg ○ 95 mmHg or higher <p>*Note that treatment must be received for a minimum of 1 year</p>
Eligibility criteria – comparator(s) / control or reference (gold) standard	Compared against each other (target versus target)
Outcomes and prioritisation	<p>All outcomes to be measured at a minimum of 12 months. Where multiple time points are reported within each study, the longest time point only will be extracted.</p> <p>Critical</p> <ul style="list-style-type: none"> ● All-cause mortality ● Health-related quality of life ● Stroke (ischaemic or haemorrhagic) ● MI <p>Important</p> <ul style="list-style-type: none"> ● Heart failure needing hospitalisation ● Vascular procedures (including lower limb, coronary and carotid artery procedures) ● Angina needing hospitalisation ● Discontinuation or dose reduction due to side effects ● Resource use ● Side effect 1: Acute kidney injury ● Side effect 2: New onset diabetes ● Side effect 3: Change in creatinine or eGFR ● Side effect 4: Hypotension (dizziness) ● [Combined cardiovascular disease outcomes in the absence of MI and stroke data] ● [Coronary heart disease outcome in the absence of MI data]
Eligibility criteria – study design	RCTs and SRs
Other inclusion exclusion criteria	<p>Exclusions:</p> <ul style="list-style-type: none"> ● Studies including participants with type 1 diabetes or chronic kidney disease (A3 [heavy proteinuria]) or A2 or above for participants with type 2 diabetes. ● Indirect populations with secondary causes of hypertension such as tumours or structural vascular defects (Conn’s adenoma, pheochromocytoma, renovascular hypertension) ● Pregnant women ● Children (under 18 years)
Proposed sensitivity / subgroup analysis, or meta-regression	<p>Subgroups for analysis of heterogeneity:</p> <ul style="list-style-type: none"> ● Age (under 55, 55–75, over 75)* ● Severity (moderate [140–159/90–99 mmHg] versus severe [\geq160/100 mmHg])

	<ul style="list-style-type: none"> • Family origin (African and Caribbean, White, South Asian) <p>*To note that evidence in those aged over 80 years if this evidence will also be analysed as a separate subgroup when reported separately.</p>
Selection process – duplicate screening / selection / analysis	A senior research fellow will undertake quality assurance prior to completion.
Data management (software)	<p>Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5).</p> <p>GRADEpro was used to assess the quality of evidence for each outcome.</p> <p>Endnote for bibliography, citations, sifting and reference management.</p>
Information sources – databases and dates	<p>Medline, Embase, the Cochrane Library</p> <p>Language: Restrict to English only</p> <p>Date cut off: from 2000</p> <p>Key papers:</p> <p>Cochrane review (2017): http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010316.pub2/full</p>
Identify if an update	Yes, 2011
Author contacts	https://www.nice.org.uk/guidance/cg127
Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for 1 database	For details, please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details, please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	<p>Standard study checklists were used to appraise individual studies critically. For details please see section 6.2 of Developing NICE guidelines: the manual</p> <p>The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the ‘Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox’ developed by the international GRADE working group http://www.gradeworkinggroup.org/</p>
Criteria for quantitative synthesis	For details, please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details, please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details, please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details, please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details, please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Anthony Wierzbicki in line with section 3 of Developing NICE guidelines: the manual.

	Staff from the NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details, please see Developing NICE guidelines: the manual.
Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds the NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered.

Table 9: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	<ul style="list-style-type: none"> • Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. No date cut-off from the previous guideline was used.
Review strategy	<p>Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the US will also be excluded.</p> <p>Studies published after 2002 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified.</p> <p>Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).⁸¹</p> <p>Inclusion and exclusion criteria</p> <ul style="list-style-type: none"> • If a study is rated as both ‘Directly applicable’ and with ‘Minor limitations’, then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either ‘Not applicable’ or with ‘Very serious limitations’, then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as ‘Partially applicable’, with ‘Potentially serious limitations’ or both, then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to exclude selectively the remaining studies. All studies excluded based on applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the US will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2002 or later (including any such studies included in the previous guideline[s]) but that depend on unit costs and resource data entirely or predominantly before 2002 will be rated as 'Not applicable'.
- Studies published before 2002 (including any such studies included in the previous guideline[s]) will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review, the more useful the analysis will be for decision-making in the guideline.
- Generally, economic evaluations based on excludes from the clinical review will be excluded.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017.

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 10: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	2000–02 October 2018	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	2000–02 October 2018	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to Issue 8 of 12, August 2018 CENTRAL to Issue 7 of 12, July 2018 DARE and NHS EED to Issue 2 of 4, April 2015 HTA to Issue 4 of 4, October 2016	None

Table 11: Medline (Ovid) search terms

1.	exp Hypertension/
2.	hypertens*.ti,ab.
3.	(elevat* adj2 blood adj pressur*).ti,ab.
4.	(high adj blood adj pressur*).ti,ab.
5.	(increase* adj2 blood pressur*).ti,ab.
6.	((systolic or diastolic or arterial) adj2 pressur*).ti,ab.
7.	or/1-6
8.	exp pregnancy/
9.	exp Hypertension, Pregnancy-Induced/ not exp Hypertension/
10.	(pre eclampsia or pre-eclampsia or preeclampsia).ti,ab.
11.	exp Hypertension, Portal/ not exp Hypertension/
12.	exp Hypertension, Pulmonary/ not exp Hypertension/
13.	exp Intracranial Hypertension/ not exp Hypertension/
14.	exp Ocular Hypertension/ not exp Hypertension/
15.	exp Diabetes Mellitus, Type 1/ not exp Diabetes Mellitus, Type 2/
16.	or/8-15
17.	7 not 16

18.	letter/
19.	editorial/
20.	news/
21.	exp historical article/
22.	Anecdotes as Topic/
23.	comment/
24.	case report/
25.	(letter or comment*).ti.
26.	or/18-25
27.	randomized controlled trial/ or random*.ti,ab.
28.	26 not 27
29.	animals/ not humans/
30.	exp Animals, Laboratory/
31.	exp Animal Experimentation/
32.	exp Models, Animal/
33.	exp Rodentia/
34.	(rat or rats or mouse or mice).ti.
35.	or/28-34
36.	17 not 35
37.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
38.	36 not 37
39.	limit 38 to English language
40.	((target* or level* or optimum or optimal or control* or tight* or strict*) adj2 (blood pressure or BP)).ti,ab.
41.	(normotensive* or normotension).ti,ab.
42.	((target* or level* or optimum or optimal) adj3 (QRISK* or Framingham or FHS or SCORE or ASSIGN or Interheart)).ti,ab.
43.	((target* or level* or optimum or optimal) adj3 ((Cardiovascular or CVD) adj3 (risk* or tool*))).ti,ab.
44.	or/40-43
45.	39 and 44
46.	randomized controlled trial.pt.
47.	controlled clinical trial.pt.
48.	randomi#ed.ti,ab.
49.	placebo.ab.
50.	randomly.ti,ab.
51.	Clinical Trials as topic.sh.
52.	trial.ti.
53.	or/46-52
54.	Meta-Analysis/
55.	exp Meta-Analysis as Topic/
56.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
57.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
58.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
59.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.

60.	(search* adj4 literature).ab.
61.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
62.	cochrane.jw.
63.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
64.	or/54-63
65.	45 and (53 or 64)

Table 12: Embase (Ovid) search terms

1.	exp Hypertension/
2.	hypertens*.ti,ab.
3.	(elevat* adj2 blood adj pressur*).ti,ab.
4.	(high adj blood adj pressur*).ti,ab.
5.	(increase* adj2 blood pressur*).ti,ab.
6.	((systolic or diastolic or arterial) adj2 pressur*).ti,ab.
7.	or/1-6
8.	exp pregnancy/
9.	exp Maternal Hypertension/
10.	(pre eclampsia or pre-eclampsia or preeclampsia).ti,ab.
11.	exp Hypertension, Portal/ not exp Hypertension/
12.	exp Hypertension, Pulmonary/ not exp Hypertension/
13.	exp Intracranial Hypertension/
14.	exp Ocular Hypertension/ not exp Hypertension/
15.	exp Diabetes Mellitus, Type 1/ not exp Diabetes Mellitus, Type 2/
16.	or/8-15
17.	7 not 16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	case report/ or case study/
22.	(letter or comment*).ti.
23.	or/18-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	nonhuman/
28.	exp Animal Experiment/
29.	exp Experimental Animal/
30.	animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice).ti.
33.	or/25-32
34.	17 not 33
35.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
36.	34 not 35
37.	limit 36 to English language
38.	((target* or level* or optimum or optimal or control* or tight* or strict*) adj2 (blood pressure or BP)).ti,ab.

39.	(normotensive* or normotension).ti,ab.
40.	((target* or level* or optimum or optimal) adj3 (QRISK* or Framingham or FHS or SCORE or ASSIGN or Interheart)).ti,ab.
41.	((target* or level* or optimum or optimal) adj3 ((Cardiovascular or CVD) adj3 (risk* or tool*))).ti,ab.
42.	or/38-41
43.	37 and 42
44.	random*.ti,ab.
45.	factorial*.ti,ab.
46.	(crossover* or cross over*).ti,ab.
47.	((doubl* or singl*) adj blind*).ti,ab.
48.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
49.	crossover procedure/
50.	single blind procedure/
51.	randomized controlled trial/
52.	double blind procedure/
53.	or/44-52
54.	systematic review/
55.	meta-analysis/
56.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
57.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
58.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
59.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
60.	(search* adj4 literature).ab.
61.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
62.	cochrane.jw.
63.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
64.	or/54-63
65.	43 and (53 or 64)

Table 13: Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Hypertension] explode all trees
#2.	hypertens*.ti,ab
#3.	(elevat* near/2 blood next pressur*).ti,ab
#4.	(high near/1 blood near/1 pressur*).ti,ab
#5.	(increase* near/2 blood pressur*).ti,ab
#6.	((systolic or diastolic or arterial) near/2 pressur*).ti,ab
#7.	(or #1-#6)
#8.	((target* or level* or optimum or optimal or control* or tight* or strict*) near/2 (blood pressure or BP)).ti,ab
#9.	(normotensive* or normotension).ti,ab
#10.	((target* or level* or optimum or optimal) near/3 (QRISK* or Framingham or FHS or SCORE or ASSIGN or Interheart)).ti,ab
#11.	((target* or level* or optimum or optimal) near/3 ((Cardiovascular or CVD) near/3 (risk* or tool*))).ti,ab
#12.	(or #8-#11)

#13.	#7 and #12
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B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating hypertension in adults population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics, economic modelling and quality of life studies.

Table 14: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014–28 August 2018	Exclusions Health economics studies
Embase	2014–28 August 2018	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception–28 August 2018 NHS EED - Inception to March 2015	None

Table 15: Medline (Ovid) search terms

1.	exp Hypertension/
2.	hypertens*.ti,ab.
3.	(elevat* adj2 blood adj pressur*).ti,ab.
4.	(high adj blood adj pressur*).ti,ab.
5.	(increase* adj2 blood pressur*).ti,ab.
6.	((systolic or diastolic or arterial) adj2 pressur*).ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice).ti.

25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	Economics/
29.	Value of life/
30.	exp "Costs and Cost Analysis"/
31.	exp Economics, Hospital/
32.	exp Economics, Medical/
33.	Economics, Nursing/
34.	Economics, Pharmaceutical/
35.	exp "Fees and Charges"/
36.	exp Budgets/
37.	budget*.ti,ab.
38.	cost*.ti.
39.	(economic* or pharmaco?economic*).ti.
40.	(price* or pricing*).ti,ab.
41.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
42.	(financ* or fee or fees).ti,ab.
43.	(value adj2 (money or monetary)).ti,ab.
44.	or/28-43
45.	27 and 44

Table 16: Embase (Ovid) search terms

1.	exp Hypertension/
2.	hypertens*.ti,ab.
3.	(elevat* adj2 blood adj pressur*).ti,ab.
4.	(high adj blood adj pressur*).ti,ab.
5.	(increase* adj2 blood pressur*).ti,ab.
6.	((systolic or diastolic or arterial) adj2 pressur*).ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	or/8-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animal/ not human/
17.	nonhuman/
18.	exp Animal Experiment/
19.	exp Experimental Animal/
20.	animal model/
21.	exp Rodent/
22.	(rat or rats or mouse or mice).ti.

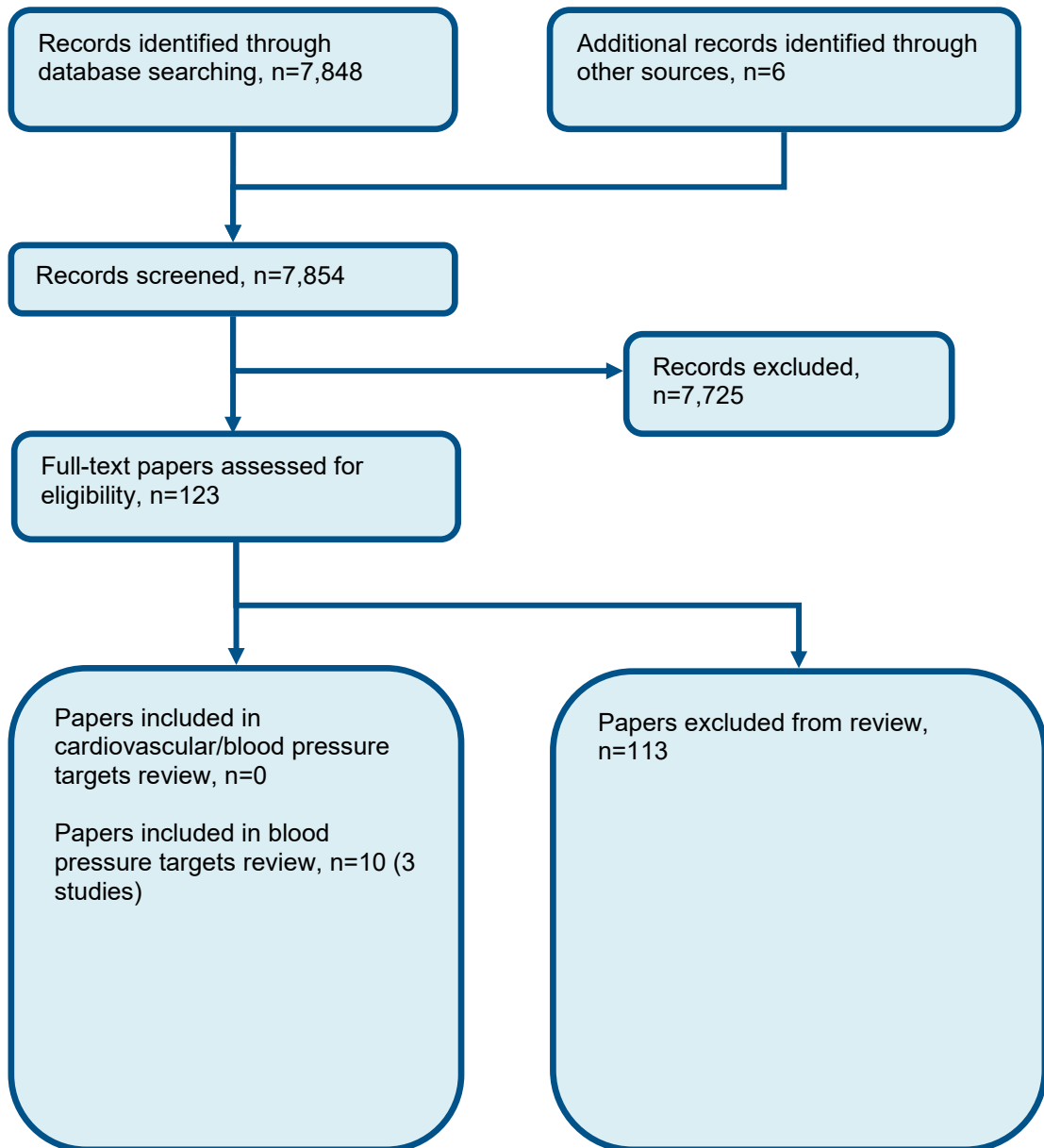
23.	or/15-22
24.	7 not 23
25.	limit 24 to English language
26.	health economics/
27.	exp economic evaluation/
28.	exp health care cost/
29.	exp fee/
30.	budget/
31.	funding/
32.	budget*.ti,ab.
33.	cost*.ti.
34.	(economic* or pharmaco?economic*).ti.
35.	(price* or pricing*).ti,ab.
36.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
37.	(financ* or fee or fees).ti,ab.
38.	(value adj2 (money or monetary)).ti,ab.
39.	or/26-38
40.	25 and 39

Table 17: NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Hypertension EXPLODE ALL TREES IN NHSEED,HTA
#2.	(Hypertens*) IN NHSEED, HTA
#3.	(elevat* adj2 blood adj pressur*) IN NHSEED, HTA
#4.	(high adj blood adj pressur*) IN NHSEED, HTA
#5.	(increase* adj2 blood pressur*) IN NHSEED, HTA
#6.	((systolic or diastolic or arterial) adj2 pressur*) IN NHSEED, HTA
#7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of targets (cardiovascular or blood pressure)



Appendix D: Clinical evidence tables

Study	Accord study group 2010 ¹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=4,733)
Countries and setting	Conducted in USA; Setting: USA and Canada, multiple centres
Line of therapy	First line
Duration of study	Intervention time: 4.7 years (mean follow up)
Method of assessment of guideline condition	Adequate method of assessment or diagnosis
Stratum	With type 2 diabetes
Subgroup analysis within study	Not stratified but pre-specified: Those with and without prior cardiovascular disease (only extracting data for those without previous CVD, 3,140 participants)
Inclusion criteria	Type 2 diabetes mellitus and a glycated haemoglobin level of 7.5% or more and were 40 years of age or older with cardiovascular disease or 55 years of age or older with anatomical evidence of a substantial amount of atherosclerosis, albuminuria, left ventricular hypertrophy, or at least 2 additional risk factors for CVD (dyslipidaemia, hypertension, smoking, or obesity). Participants with a systolic BP between 130 and 180 mmHg who were taking 3 or fewer antihypertensive medications and who had the equivalent of a 24-hour protein excretion rate of less than 1.0 g were also eligible for the blood-pressure trial
Exclusion criteria	Body mass index (the weight in kilograms divided by the square of the height in meters) of more than 45, a serum creatinine level of more than 1.5 mg per decilitre (132.6 µmol per litre), and other serious illness.
Recruitment/selection of patients	77 clinical sites
Age, sex and family origin	Age - Mean (SD): 62.2 years (6.9). Sex (M:F): 2475:2258. Family origin: 60.5% Non-Hispanic White, 24.1 Black, 7% Hispanic
Further population details	1. Age: Not stated / Unclear 2. Family origin: Not stated / Unclear 3. Severity: Not applicable
Extra comments	Participants also randomised to either intensive or standard glycaemic control in a 2x2 factorial design.
Indirectness of population	No indirectness
Interventions	(n=1,558) Intervention 1: Systolic BP targets - <120 mmHg. For participants in the intensive-therapy group, visits to assess BP were scheduled once a month for 4 months and every 2 months thereafter. Additional visits were scheduled as needed in both groups to monitor and ensure appropriate implementation of the

	<p>study intervention strategies. In both blood-pressure groups, participants who were assigned to intensive glycaemic therapy had more frequent contacts for the management of glycaemia, but blood pressure was not monitored at these additional visits. However, all the antihypertensive regimens were to include drug classes that had been shown to result in a reduction in cardiovascular events among participants with diabetes. Participants in the intensive arm of the trial initiated treatment with a diuretic and either an angiotensin-converting enzyme (ACE) inhibitor or a beta-blocker. Other drugs added were calcium channel blockers (CCB), other diuretics and angiotensin receptor blockers (ARB). Blood pressure measured using an automated device (Omron 907) after 5 minutes rest with the participant seated in a chair (average of 3 measurements).</p> <p>Duration 4.7 years. Concurrent medication or care: Participants were also randomised to glycaemic control (intensive or standard; intensive therapy targeted a glycated haemoglobin level below 6.0%, standard therapy targeted a level from 7.0 to 7.9%).</p> <p>Indirectness: No indirectness</p> <p>(n=1,582) Intervention 2: Systolic BP targets – 130–139 mmHg. Visits were scheduled at months 1 and 4 and every 4 months thereafter. Additional visits were scheduled as needed in both groups to monitor and ensure appropriate implementation of the study intervention strategies. In both blood-pressure groups, participants who were assigned to intensive glycaemic therapy had more frequent contacts for the management of glycaemia, but blood pressure was not monitored at these additional visits. For standard BP group participants, medication dose titration or addition of another drug was indicated if systolic BP was >160 mmHg at a single visit or >140 mmHg at 2 successive visits. Down-titration was encouraged if systolic BP was <135 mmHg on 2 successive visits or <130 mmHg at any single visit. All antihypertensive regimens were to include a drug class that had demonstrated reduced cardiovascular events in participants with diabetes: diuretic, beta-blocker, CCB, ACE inhibitor, or ARB. Blood pressure measured using an automated device (Omron 907) after 5 minutes rest with the participant seated in a chair (average of 3 measurements). Duration 4.7 years. Concurrent medication or care: Also randomised to intensive therapy (targeting a glycated haemoglobin level below 6.0%) or standard therapy (targeting a level from 7.0 to 7.9%).</p> <p>Indirectness: No indirectness</p>
Funding	Academic or government funding (National Heart, Lung, and Blood Institute)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: <120 mmHg versus <140 mmHg	
<p>Protocol outcome 1: Stroke (ischaemic or haemorrhagic)</p> <p>- Actual outcome for with type 2 diabetes: Stroke (non-fatal), MI (non-fatal), CVD (fatal) at 1 year (outcomes given on a per year basis); Group 1: 21/1,558; Group 2: 23/1,582</p> <p>Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness</p>	
Protocol outcomes not reported by the	All-cause mortality; Health-related quality of life; MI; Heart failure needing hospitalisation; Vascular

study	procedures (including lower limb, coronary and carotid artery procedures); Angina needing hospitalisation; Discontinuation or dose reduction due to side effects; Resource use; Acute kidney injury; New onset diabetes; Change in creatinine or eGFR; Hypotension (dizziness)
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Study	Verdecchia 2009 ¹¹⁶
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=1,111)
Countries and setting	Conducted in Italy; Setting: 44 centres across Italy
Line of therapy	First line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Hypertension diagnosis
Stratum	Without type 2 diabetes
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Systolic BP of 150 mmHg or over (2) taking antihypertensive treatment for at least 12 weeks (3) 1 additional risk factor as described in the guidelines of ESH
Exclusion criteria	(1) Fasting glucose level of 7 mmol/L or higher (2) any other disease reducing life expectancy (3) renal dysfunction (4) clinically relevant hepatic or haematological disorders (5) heart conditions and other conditions confusing the electrocardiogram (ECG) diagnosis of left ventricular hypertrophy (LVH). (6) substance misuse
Recruitment/selection of patients	22 Feb 2005 to 28 Feb 2007
Age, sex and family origin	Age - Mean (SD): 67(7) years. Sex (M:F): 437:653. Family origin: Not specified
Further population details	1. Age: Systematic review: mixed (55 and older). 2. Family origin: Not stated / Unclear 3. Severity: Not stated / Unclear (Mixed).
Indirectness of population	No indirectness
Interventions	(n=553) Intervention 1: Systolic blood pressure targets – 130–139 mmHg. Run in period to ensure systolic BP remained above 150 mmHg at 2 visits 7–14 days apart. Participants were followed every 4 months for 2 years. At each visit, physicians measured blood pressure by auscultation, with a standard mercury sphygmomanometer, after participants had been seated for 10 minutes. Treatment involved various combinations of previous drugs with the addition of furosemide (25 mg per day), Ramipril (5 mg or 10 mg per day), telmisartan (80 mg per day), amlodipine (5 mg or 10 mg per day), bisoprolol (5 mg per day), and transdermal clonidine (2.5 mg or 5.0 mg per day). Ramipril and telmisartan were also available in fixed combinations with hydrochlorothiazide (12.5 mg or 25.0 mg per day for Ramipril, and 12.5 mg per day for telmisartan). At every visit, the choice of drugs in individual people was left to the discretion of the investigators. Achievement of a systolic blood pressure below 130 mmHg entailed down titration of treatment. Duration 2 years. Concurrent medication/care: 23% Statins, 19% Aspirin. Indirectness: No indirectness

	<p>(n=558) Intervention 2: Systolic blood pressure targets – 120–129 mmHg. Run in period to ensure systolic BP remained above 150 mmHg at 2 visits 7–14 days apart. Participants were followed every 4 months for 2 years. At each visit, physicians measured blood pressure by auscultation, with a standard mercury sphygmomanometer, after participants had been seated for 10 minutes. Treatment involved various combinations of previous drugs with the addition of furosemide (25 mg per day), Ramipril (5 mg or 10 mg per day), telmisartan (80 mg per day), amlodipine (5 mg or 10 mg per day), bisoprolol (5 mg per day), and transdermal clonidine (2.5 mg or 5.0 mg per day). Ramipril and telmisartan were also available in fixed combinations with hydrochlorothiazide (12.5 mg or 25.0 mg per day for Ramipril, and 12.5 mg per day for telmisartan). At every visit, the choice of drugs in individual people was left to the discretion of the investigators. One systolic blood-pressure reading higher than 130 mmHg at any visit led to intensification of treatment. Duration 2 years. Concurrent medication/care: 22% on Statins and 19% aspirin. Indirectness: No indirectness</p>
<p>Funding</p>	<p>Study funded by industry (Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO) through grants from Boehringer-Ingelheim, Sanofi-Aventis, and Pfizer to ANMCOv)</p>
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: 130–139 mmHg versus 120–129 mmHg</p> <p>Protocol outcome 1: All-cause mortality - Actual outcome for Without type 2 diabetes: Death at 2 years; Group 1: 5/553, Group 2: 4/558 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Previous CV disease not reported;</p> <p>Protocol outcome 2: Stroke (ischaemic or haemorrhagic) - Actual outcome for Without type 2 diabetes: Stroke or transient ischaemic attack (TIA) at 2 years; Group 1: 9/583, Group 2: 4/558 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Previous CV disease not reported;</p> <p>Protocol outcome 3: Myocardial infarction - Actual outcome for Without type 2 diabetes: Myocardial infarction at 2 years; Group 1: 6/553, Group 2: 4/558 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Previous CV disease not reported</p> <p>Protocol outcome 4: Heart failure needing hospitalisation - Actual outcome for Without type 2 diabetes: Admission for heart failure at 2 years; Group 1: 7/553, Group 2: 3/558 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Previous CV disease not reported</p>	

Protocol outcome 5: Vascular procedures (including lower limb, coronary and carotid artery procedures)
 - Actual outcome for Without type 2 diabetes: Coronary revascularization at 2 years; Group 1: 15/553, Group 2: 5/558
 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Previous CV disease not reported;

Protocol outcome 6: Resource use
 - Actual outcome for without type 2 diabetes: Mean systolic blood pressure reduction (average from all visits) at 2 years; Group 1: mean 23.5 mmHg (SD 10.6); n=553, Group 2: mean 27.3 mmHg (SD 11); n=558; Comments: Estimate standard deviation (SD) from p value <0.0001
 Risk of bias: All domain - ; Indirectness of outcome: No indirectness
 - Actual outcome for without type 2 diabetes: Mean diastolic blood pressure reduction (average in all visits) at 2 years; Group 1: mean 8.9 mmHg (SD 7); n=553, Group 2: mean 10.4 mmHg (SD 7.5); n=558
 Risk of bias: All domain - ; Indirectness of outcome: No indirectness

Protocol outcome 7: Hypotension (dizziness)
 - Actual outcome for without type 2 diabetes: Dizziness at 2 years; Group 1: 4/553, Group 2: 2/558
 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Previous CVD not reported;

Protocol outcomes not reported by the study	Health-related quality of life; Angina needing hospitalisation; Discontinuation or dose reduction due to side effects; Acute kidney injury; New onset diabetes; Change in creatinine or eGFR
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Study (subsidiary papers)	SPRINT Study Group 2015: Wright 2015¹²³; Ambrosius 2014²; 20, 31, 84, 95
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=9,361 [6,715 without CKD analysed])
Countries and setting	Conducted in USA; Setting: 102 clinical sites in the US
Line of therapy	First line
Duration of study	Intervention time: Median 3.26 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: >50 years
Stratum	Without type 2 diabetes
Subgroup analysis within study	Not applicable
Inclusion criteria	Participants were required to meet all the following criteria: an age of at least 50 years, a systolic blood pressure of 130 to 180 mmHg (see the Supplementary appendix), and an increased risk of cardiovascular events. Increased cardiovascular risk was defined by 1 or more of the following: clinical or subclinical CVD other than stroke; CKD, excluding polycystic kidney disease, with an estimated glomerular filtration rate (eGFR) of 20 to less than 60 ml per minute per 1.73 m ² of body-surface area, calculated with the use of the 4-variable Modification of Diet in Renal Disease equation; a 10-year risk of cardiovascular disease of 15% or greater on the basis of the Framingham risk score; or an age of 75 years or older.
Exclusion criteria	People with diabetes mellitus or prior stroke were excluded. People with other severe health conditions that could influence the study were excluded (such as cancer, diagnosed within the last 2 years).
Recruitment/selection of patients	From 2010 to 2013. SPRINT also recruited from nested sub-studies: SPRINT MIND and SPRINT MIND MRI.
Age, sex and family origin	Age – Mean: 66.3 (9) years Sex (M:F)4418:2244. Family origin: 32% Black, 54% non-Hispanic white, 11.8% Hispanic, 2.2% other
Further population details	1. Age: Systematic review: mixed 2. Family origin: Systematic review: mixed 3. Severity: Systematic review: mixed
Indirectness of population	No indirectness
Interventions	(n=3,348) Intervention 1: Systolic blood pressure targets - <120 mmHg. Achieved average blood pressure 119 mmHg. The protocol recommended that antihypertensive regimens should include 1 or more drug classes with the strongest evidence for capacity to prevent CVD outcomes: thiazide-type diuretics, CCBs, ACE inhibitors, and ARBs, with priority for prescription of thiazide-type diuretics. In both groups, participants are evaluated monthly for the first 3 months, and thereafter every 3 months. Monthly visits continue in the Intensive Group until a systolic blood pressure <120 mmHg is achieved or no more titration is planned and in the Standard Group whenever a systolic blood pressure ≥160 mmHg is noted. Additional visits can be

scheduled as needed for monitoring medications and safety. For most participants in the Intensive Group, a 2- or 3-drug regimen was initiated at randomization (occasionally only 1 drug for participants ≥ 75 years). Drug doses are increased or additional antihypertensive medications are added at monthly visits until the target of <120 mmHg is reached or the investigator decides no further antihypertensive medications should be added. "Milepost Visits" are scheduled every 6 months. If the systolic blood pressure is not <120 mmHg at a Milepost Visit, an antihypertensive drug from an additional class is added, absent contraindications. For Standard Group participants, the protocol is designed to achieve a systolic blood pressure of 135–139 mmHg, starting with the randomization visit. Dose titration or addition of another drug occurs if systolic blood pressure is ≥ 160 mmHg at a single visit or ≥ 140 mmHg at 2 successive visits. Medication may be reduced if the systolic blood pressure is <130 mmHg at a single visit or <135 mmHg at 2 consecutive visits. Titration of medications to target is based on a mean of 3 office blood pressure measurements obtained in the seated position using an automated measurement device (Omron Healthcare, Lake Forest, IL, USA). Blood pressure is also measured 1 minute after standing at screening, baseline, 1 month, 6 months, 12 months, and annually thereafter. While standing, participants are asked about symptoms of hypotension (see Safety section).

Actual strategy for blood pressure measurement varied within SPRINT. The majority of participants ($n=4,082$) were always alone when their blood pressure was measured. 2,247 participants were never alone, 1,746 were alone for the rest period and 570 were alone for blood pressure measurement. Blood pressure did not appear to differ between the groups.

Duration 3.26 years. Concurrent medication or care: All participants are advised to follow lifestyle recommendations and background therapy consistent with current practice guidelines to minimize differences in the effects of nonstudy strategies that could influence systolic BP or CVD outcomes in the 2 treatment arms. Specific lifestyle recommendations include weight loss for overweight participants, a heart-healthy diet (for example, the DASH diet) with appropriate modifications for participants with CKD, reducing sodium intake and alcohol consumption below maximum recommended levels, regular aerobic exercise, and smoking cessation. Indirectness: No indirectness

($n=3,367$) Intervention 2: Systolic blood pressure targets – 130–139 mmHg. Mean achieved BP of 134 mmHg. Titration of medications to target is based on a mean of 3 office blood pressure measurements obtained in the seated position using an automated measurement device (Omron Healthcare, Lake Forest, IL, USA). Blood pressure is also measured 1 minute after standing at screening, baseline, 1 month, 6 months, 12 months, and annually thereafter. For Standard Group participants, the protocol is designed to achieve a systolic blood pressure of 135–139 mmHg, starting with the randomization visit. Dose titration or addition of another drug occurs if systolic blood pressure is ≥ 160 mmHg at a single visit or ≥ 140 mmHg at 2 successive visits. Medication may be reduced if the systolic blood pressure is <130 mmHg at a single visit or <135 mmHg at 2 consecutive visits. In both groups, participants are evaluated monthly for the first 3 months,

	<p>and thereafter every 3 months. Monthly visits continue in the Intensive Group until a systolic BP <120 mmHg is achieved or no more titration is planned and in the Standard Group whenever a systolic BP ≥160 mmHg is noted. Additional visits can be scheduled as needed for monitoring medications and safety. The protocol recommended that antihypertensive regimens should include 1 or more drug classes with the strongest evidence for capacity to prevent CVD outcomes: thiazide-type diuretics, CCBs, ACE inhibitors, and ARBs, with priority for prescription of thiazide-type diuretics. Actual strategy for BP measurement varied within SPRINT. The majority of participants (n=4,082) were always alone when their blood pressure was measured. 2,247 participants were never alone, 1,746 were alone for the rest period and 570 were alone for blood pressure measurement. Blood pressure did not appear to differ between the groups</p> <p>Duration 3.26 years. Concurrent medication/care: All participants are advised to follow lifestyle recommendations and background therapy consistent with current practice guidelines to minimize differences in the effects of non-study strategies that could influence systolic BP or CVD outcomes in the 2 treatment arms. Specific lifestyle recommendations include weight loss for overweight participants, a heart-healthy diet (for example, the DASH diet) with appropriate modifications for participants with CKD, reducing sodium intake and alcohol consumption below maximum recommended levels, regular aerobic exercise, and smoking cessation. Indirectness: No indirectness</p>
Funding	Academic or government funding (NIH)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: <120 mmHg versus 130–139 mmHg</p>	
<p>Protocol outcome 1: All-cause mortality at 3.26 years</p>	
<p>- Actual outcome for without type 2 diabetes: All-cause mortality at 3.26 years; Group 1: 85/3,348, Group 2: 115/3,367</p>	
<p>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 168; Group 2 Number missing: 169</p>	
<p>Protocol outcome 2: Stroke (ischaemic or haemorrhagic) at 3.26 years</p>	
<p>- Actual outcome for without type 2 diabetes: Stroke at 3.26 years; Group 1: 35/3,348, Group 2: 43/3,367</p>	
<p>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 168; Group 2 Number missing: 169</p>	
<p>Protocol outcome 3: Myocardial infarction at 3.26 years</p>	
<p>- Actual outcome for without type 2 diabetes: MI at 3.26 years; Group 1: 53/3,348, Group 2: 71/3,367</p>	
<p>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 168; Group 2 Number missing: 169</p>	
<p>Protocol outcome 4: Heart failure needing hospitalisation at 3.26 years</p>	
<p>- Actual outcome for without type 2 diabetes: Heart failure at 3.26 years; Group 1: 21/3,348, Group 2: 48/3,367</p>	

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 168; Group 2 Number missing: 169

Protocol outcome 5: Resource use at 3.26 years

- Actual outcome for without type 2 diabetes: Mean reduction in systolic blood pressure at 6 months (graph depicts no change after this point); MD; 15 (95%CI 14.7 to 15.4, Units: mmHg, Comments: Baseline values: <120mmHg target: 139.9 [15.6], <140mmHg target: 139.8 [15.1]); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Very serious indirectness; Group 1 Number missing: 168; Group 2 Number missing: 169

- Actual outcome for without type 2 diabetes: Mean number of medications at 2 years at 2 years; Group 1: mean 2.8 Number of pills (SD 1.2); n=3,348, Group 2: mean 1.8 Number of pills (SD 1.1); n=3,367; Comments: Mean at baseline I: 1.74(1.03) and S: 1.72 (1.04) in the 89% already taking antihypertensive medication

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Very serious indirectness; Group 1 Number missing: 168; Group 2 Number missing: 169

Protocol outcome 6: Acute kidney injury at 3.26 years

- Actual outcome for without type 2 diabetes: Acute kidney injury at 3.26 years; Group 1: 82/3,348, Group 2: 38/3,367

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 168; Group 2 Number missing: 169

Stage 1, 2 and 3 AKI as defined in Rocco 2018

Protocol outcome 7: Change in creatinine or eGFR at 3.26 years

- Actual outcome for without type 2 diabetes: >30% reduction in eGFR at 3.26 years; Group 1: 140/3,348, Group 2: 40/3,367; Comments: Also taken from Anim paper

HR per 100 patient years 3.54 (2.50 to 5.02)

mean eGFR at baseline (ml/min/1.73m³)

Intensive: 81.3 (15.5)

Standard: 81.2 (15.5)

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 168; Group 2 Number missing: 169

- Actual outcome for without type 2 diabetes: >30% reduction in eGFR to <60ml/min/1.73m³ at 3.26 years; Group 1: 127/3,332, Group 2: 37/3,345

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 168; Group 2 Number missing: 169

Protocol outcome 8: Hypotension (dizziness) at 3.26 years

- Actual outcome for without type 2 diabetes: Hypotension at 3.26 years; Group 1: 59/3348, Group 2: 28/3367

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

<p>Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 168; Group 2 Number missing: 169 - Actual outcome for without type 2 diabetes: Orthostatic hypotension (with dizziness) at 3.26 years; Group 1: 38/3,348, Group 2: 48/3,367 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 168; Group 2 Number missing: 169 - Actual outcome for without type 2 diabetes: Orthostatic hypotension (without dizziness) at 3.26 years; Group 1: 476/3,348, Group 2: 555/3,367 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 168; Group 2 Number missing: 169 Protocol outcome 8: Hypotension (dizziness) - Actual outcome for without type 2 diabetes: Syncope at 3.26 years; Group 1: 109/3,348, Group 2: 71/3,367 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 168; Group 2 Number missing: 169 - Actual outcome for without type 2 diabetes: Injurious falls at 3.26 years; Group 1: 104/3,348, Group 2: 84/3,367 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 168; Group 2 Number missing: 169</p>	
<p>Protocol outcomes not reported by the study</p>	<p>Health-related quality of life; Vascular procedures (including lower limb, coronary and carotid artery procedures); Angina needing hospitalisation; Discontinuation or dose reduction due to side effects; New onset diabetes</p>

Appendix E: Forest plots

E.1 Below 120 mmHg versus below 140 mmHg (non-diabetic population)

Figure 2: All-cause mortality at 3.26 years

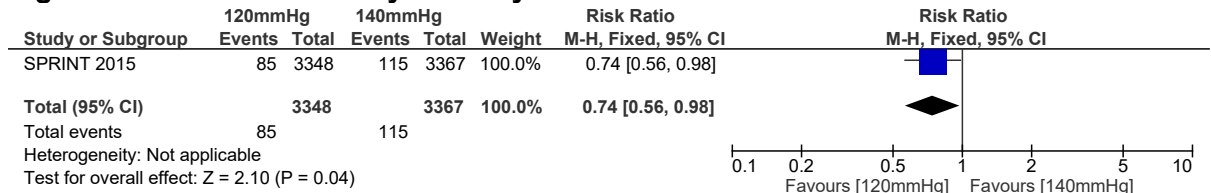


Figure 3: Stroke at 3.26 years

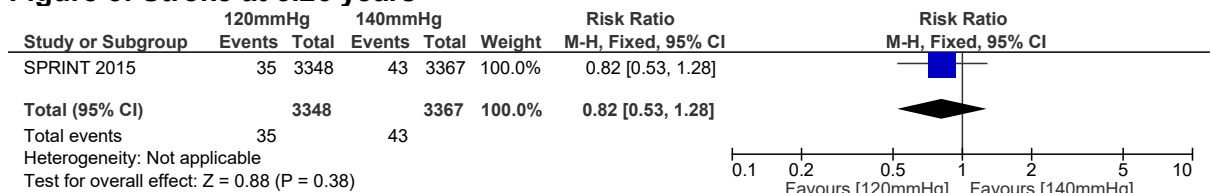


Figure 4: Myocardial infarction at 3.26 years

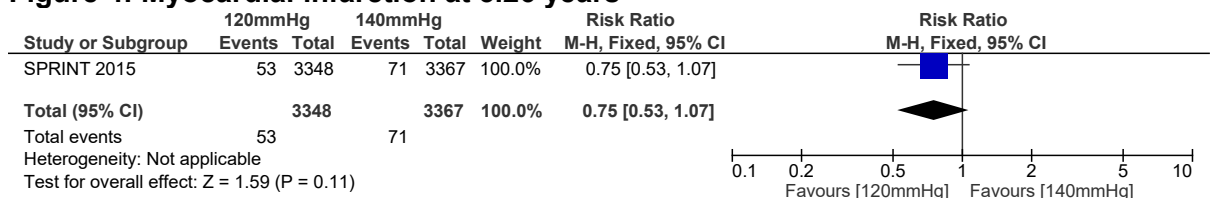


Figure 5: Heart failure at 3.26 years

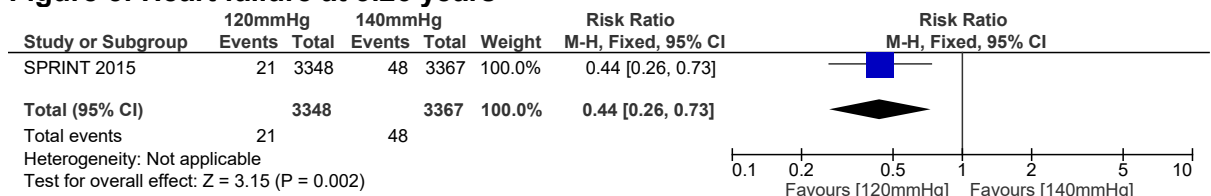


Figure 6: Acute kidney injury at 3.26 years

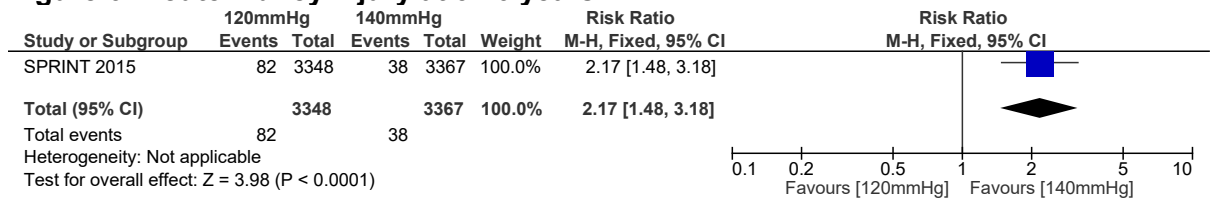


Figure 7: More than 30% reduction in eGFR at 3.26 years

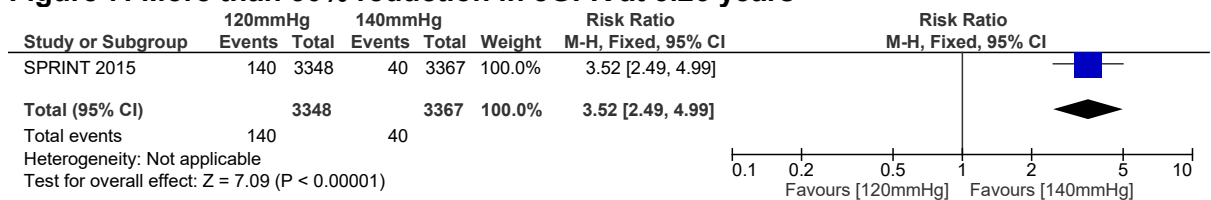


Figure 8: Hypotension at 3.26 years

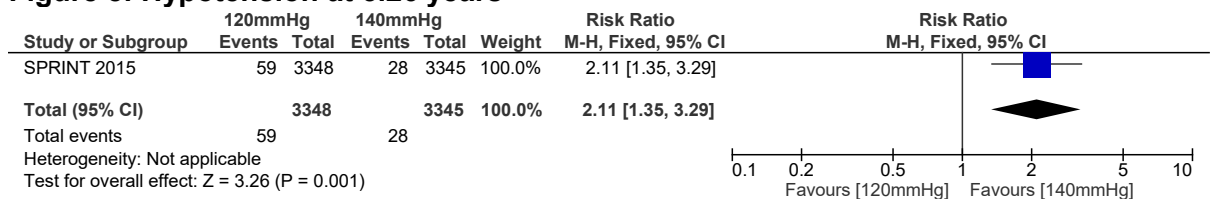


Figure 9: Orthostatic hypotension with dizziness at 3.26 years

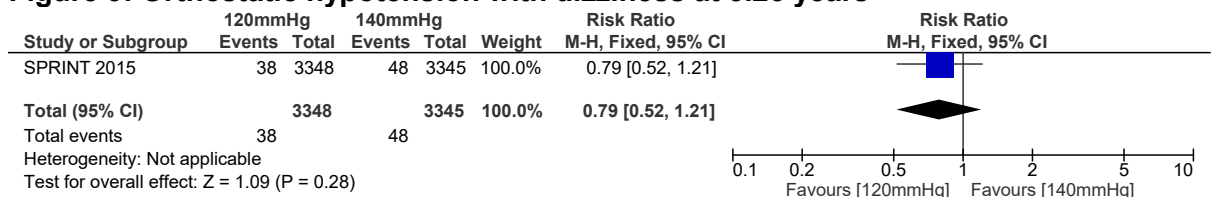


Figure 10: Orthostatic hypotension without dizziness at 3.26 years

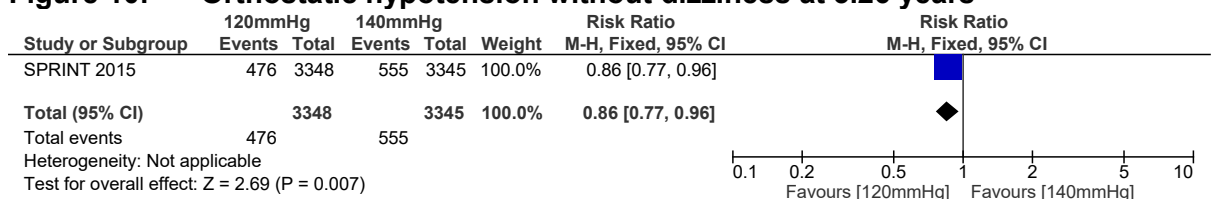


Figure 11: Syncope at 3.16 years

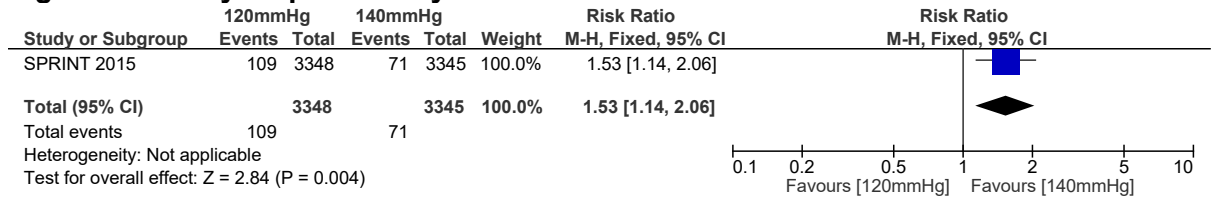


Figure 12: Injurious falls at 3.26 years

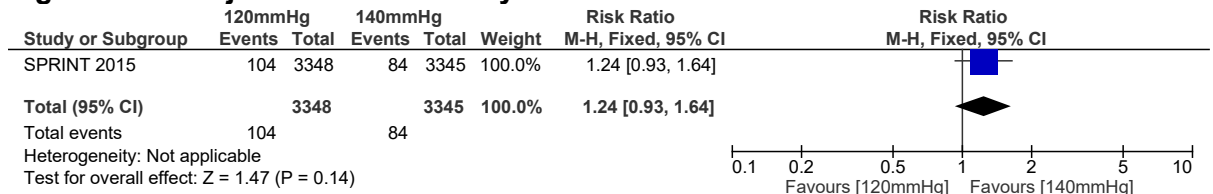


Figure 13: Mean reduction in systolic blood pressure at 6 months

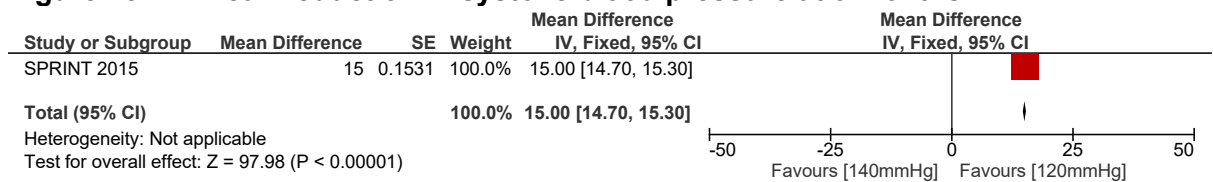
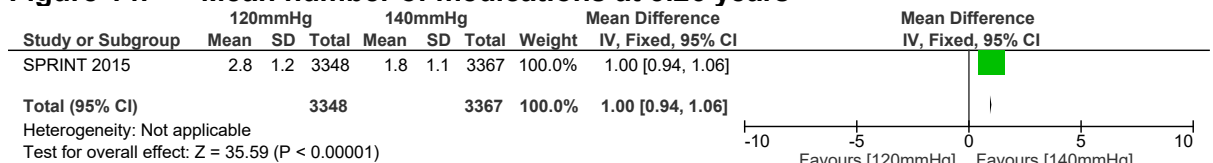


Figure 14: Mean number of medications at 3.26 years



E.2 Below 120 mmHg versus below 140 mmHg (diabetic population)

Figure 15: Stroke (non-fatal), myocardial infarction (non-fatal), cardiovascular disease (fatal) at 4.7 years



E.3 Below 130 mmHg versus below 140 mmHg (non-diabetic population)

Figure 16: All-cause mortality at 2 years

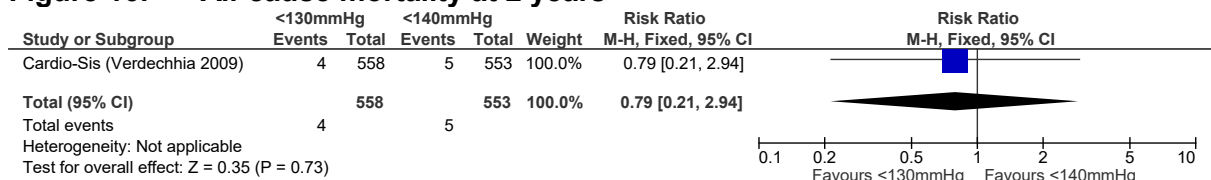


Figure 17: Stroke at 2 years



Figure 18: Myocardial infarction at 2 years

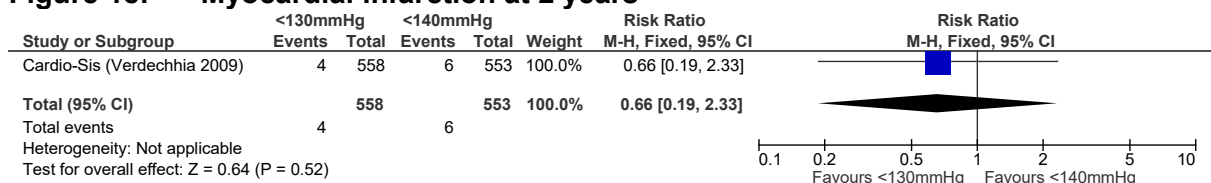


Figure 19: Heart failure requiring hospitalisation at 2 years

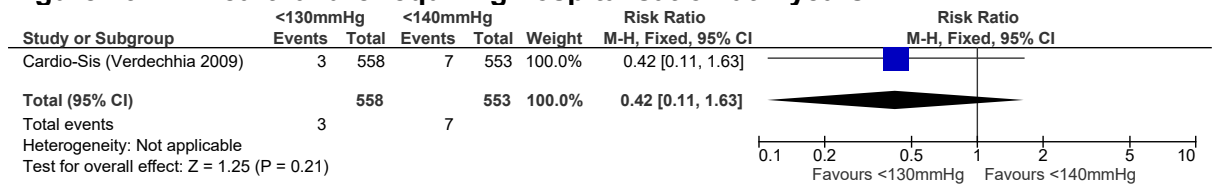


Figure 20: Dizziness at 2 years

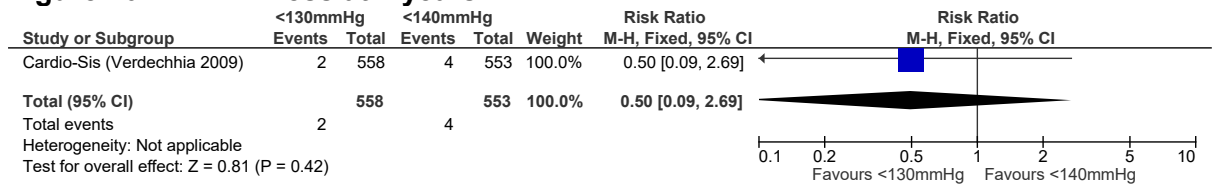
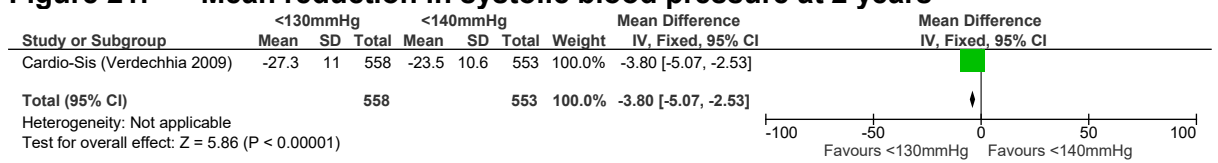


Figure 21: Mean reduction in systolic blood pressure at 2 years



Appendix F: GRADE tables

Table 18: Clinical evidence summary: Below 120 mmHg versus below 140 mmHg (non-diabetic population)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	120mmHg versus 140mmHg	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up median 3.26 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious ¹	Serious ²	none	85/3348 (2.5%)	115/3367 (3.4%)	RR 0.74 (0.56 to 0.98)	9 fewer per 1000 (from 1 fewer to 15 fewer)	⊕⊕⊕⊕ LOW	CRITICAL
Stroke (follow-up median 3.26 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious ¹	very serious ²	none	35/3348 (1%)	43/3367 (1.3%)	RR 0.82 (0.53 to 1.28)	2 fewer per 1000 (from 6 fewer to 4 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
Myocardial infarction (follow-up median 3.26 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious ¹	Serious ²	none	53/3348 (1.6%)	71/3367 (2.1%)	RR 0.75 (0.53 to 1.07)	5 fewer per 1000 (from 10 fewer to 1 more)	⊕⊕⊕⊕ LOW	CRITICAL
Heart failure (follow-up median 3.26 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious ¹	no serious imprecision	none	21/3348 (0.63%)	48/3367 (1.4%)	RR 0.44 (0.26 to 0.73)	8 fewer per 1000 (from 4 fewer to 11 fewer)	⊕⊕⊕⊕ MODERATE	IMPORTANT
Acute kidney injury (follow-up median 3.26 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious ¹	no serious imprecision	none	82/3348 (2.4%)	38/3367 (1.1%)	RR 2.17 (1.48 to 3.18)	13 more per 1000 (from 5 more to 25)	⊕⊕⊕⊕ MODERATE	IMPORTANT

										more)		
>30% reduction in eGFR (follow-up median 3.26 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious ¹	no serious imprecision	none	140/3348 (4.2%)	40/3367 (1.2%)	RR 3.52 (2.49 to 4.99)	30 more per 1000 (from 18 more to 47 more)	⊕⊕⊕⊕ MODERATE	IMPORTANT
Hypotension (follow-up median 3.26 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious ¹	no serious imprecision	none	59/3348 (1.8%)	28/3345 (0.84%)	RR 2.11 (1.35 to 3.29)	9 more per 1000 (from 3 more to 19 more)	⊕⊕⊕⊕ MODERATE	IMPORTANT
Orthostatic hypotension with dizziness (follow-up median 3.26 years)												
1	no methodology chosen	no serious risk of bias	no serious inconsistency	serious ¹	Serious ²	none	38/3348 (1.1%)	48/3345 (1.4%)	RR 0.79 (0.52 to 1.21)	3 fewer per 1000 (from 7 fewer to 3 more)	⊕⊕⊕⊕ LOW	IMPORTANT
Orthostatic hypotension without dizziness (follow-up median 3.26 years)												
1	no methodology chosen	no serious risk of bias	no serious inconsistency	serious ¹	Serious ²	none	476/3348 (14.2%)	555/3345 (16.6%)	RR 0.86 (0.77 to 0.96)	23 fewer per 1000 (from 7 fewer to 38 fewer)	⊕⊕⊕⊕ LOW	IMPORTANT
Syncope (follow-up median 3.26 years)												
1	no methodology chosen	no serious risk of bias	no serious inconsistency	serious ¹	Serious ²	none	109/3348 (3.3%)	71/3345 (2.1%)	RR 1.53 (1.14 to 2.06)	11 more per 1000 (from 3 more to 22 more)	⊕⊕⊕⊕ LOW	IMPORTANT
Injurious falls (follow-up median 3.26 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious ¹	Serious ²	none	104/3348 (3.1%)	84/3345 (2.5%)	RR 1.24 (0.93 to 1.64)	6 more per 1000 (from 2 fewer to 16 more)	⊕⊕⊕⊕ LOW	IMPORTANT
Mean blood pressure (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of	no serious inconsistency	very serious ²	no serious imprecision	none	3348	3367	-	MD 15mmHg lower (14.7 to	⊕⊕⊕⊕ LOW	IMPORTANT

		bias								15.4 higher)		
Mean number of medications (follow-up median 3.26 years; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious ¹	no serious imprecision	none	3348	3367	-	MD 1 higher (0.94 to 1.06 higher)	⊕⊕⊕⊕ LOW	IMPORTANT

¹ The majority of the evidence included an indirect outcome or intervention (downgrade by 1 increment) or a very indirect outcome or intervention (downgrade by 2 increments)

² Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 19: Clinical evidence summary: Below 120 mmHg versus below 140mmHg (diabetic population)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	120mmHg versus 140mmHg (diabetic population)	Control	Relative (95% CI)	Absolute		
Stroke (non-fatal), myocardial infarction (non-fatal), cardiovascular disease (fatal; follow-up median 3.26 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Very serious ¹	none	21/1558 (1.3%)	23/1582 (1.5%)	RR 0.93 (0.52 to 1.67)	1 fewer per 1000 (from 7 fewer to 10 more)	⊕⊕⊕⊕ LOW	CRITICAL

¹ Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 20: Clinical evidence summary: Below 130 mmHg versus below 140 mmHg (non-diabetic population)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	<130mmHg versus <140mmHg (non-diabetic population)	Control	Relative (95% CI)	Absolute		
All-cause mortality at 2 years (follow-up mean 2 years)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Very serious ¹	none	4/558 (0.72%)	5/553 (0.9%)	RR 0.79 (0.21 to 2.94)	2 fewer per 1000 (from 7 fewer to 18 more)	⊕⊕⊕⊕ LOW	CRITICAL
Stroke at 2 years (follow-up mean 2 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Very serious ¹	none	4/558 (0.72%)	9/583 (1.5%)	RR 0.46 (0.14 to 1.5)	8 fewer per 1000 (from 13 fewer to 8 more)	⊕⊕⊕⊕ LOW	CRITICAL
Myocardial infarction at 2 years (follow-up mean 2 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Very serious ¹	none	4/558 (0.72%)	6/553 (1.1%)	RR 0.66 (0.19 to 2.33)	4 fewer per 1000 (from 9 fewer to 14 more)	⊕⊕⊕⊕ LOW	CRITICAL
Heart failure admission at 2 years (follow-up mean 2 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Very serious ¹	none	3/558 (0.54%)	7/553 (1.3%)	RR 0.42 (0.11 to 1.63)	7 fewer per 1000 (from 11 fewer to 8 more)	⊕⊕⊕⊕ LOW	IMPORTANT
Dizziness at 2 years (follow-up mean 2 years)												
1	randomised trials	serious ²	no serious inconsistency	serious ³	Very serious ¹	none	2/558 (0.36%)	4/553 (0.72%)	RR 0.5 (0.09 to 2.69)	4 fewer per 1000 (from 7 fewer to 12 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
Mean reduction in blood pressure (follow-up mean 2 years; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	558	553	-	MD 3.8 lower (5.07 to 2.53 lower)	⊕⊕⊕⊕ MODERATE	IMPORTANT

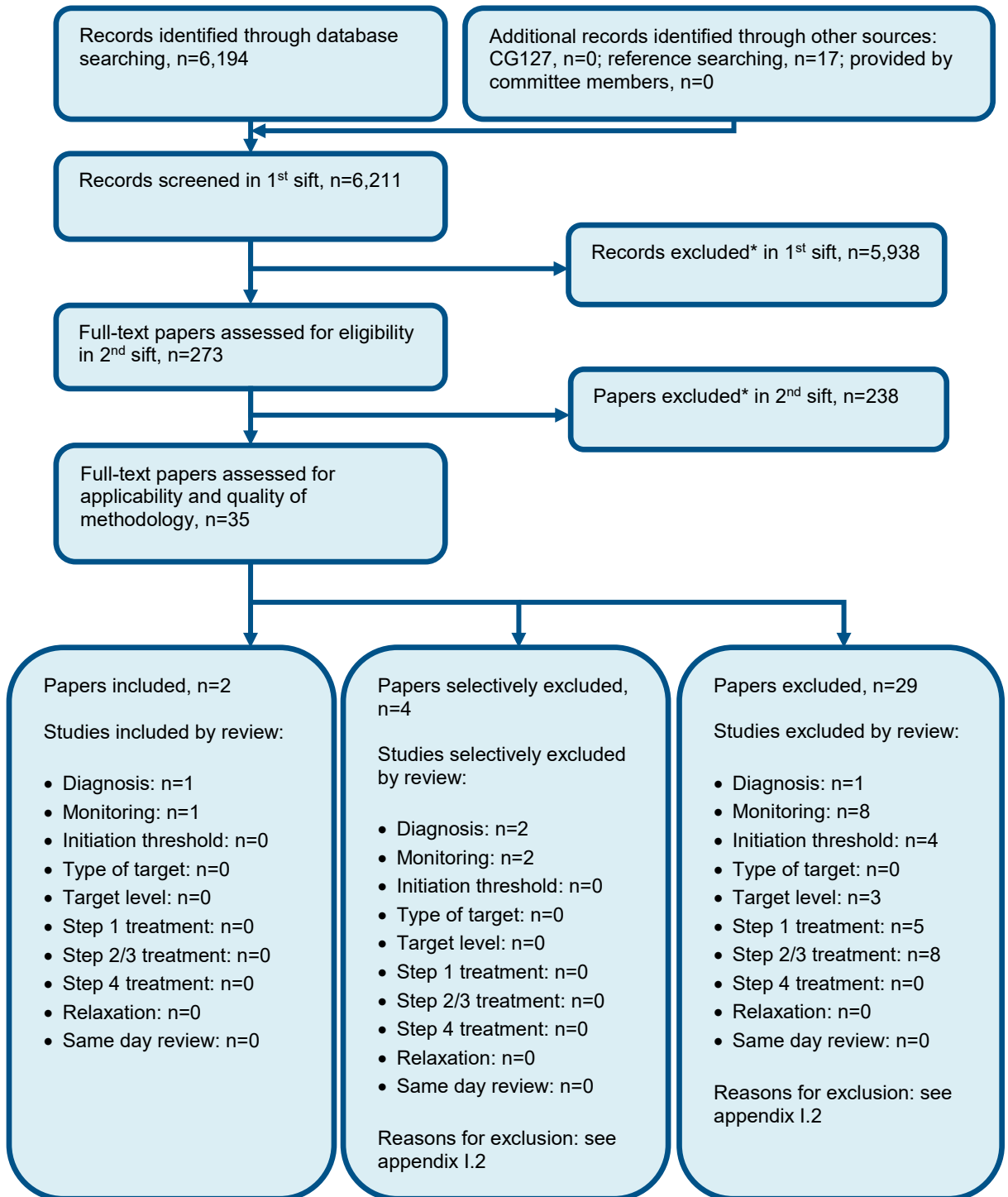
¹ Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

² Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

³ The majority of the evidence included an indirect outcome (downgraded by 1 increment) or a very indirect outcome (downgraded by 2 increments)

Appendix G: Health economic evidence selection

Figure 22: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Study (ID)	Exclusion reason
Arima 2006 ⁷	Incorrect population. Population had a history of cerebrovascular disease
BPLTTC 2008 ²⁴	Systematic review, references checked
Coca 2008 ³⁵	Incorrect population. Population had coronary artery disease
Denardo 2010. ³⁸	Incorrect comparison, incorrect analysis. Secondary analysis of INVEST trial comparing participants on varapamil or atenolol based treatment.
Fagard 2007 ⁴²	Incorrect study design. Prognostic study predicting cardiovascular revents based on diastolic blood pressure
Hosohata 2007 ⁵¹	No relevant outcomes
Ichihara 2003 ⁵⁴	No relevant outcomes
JATOS Study Group 2005 ⁵⁹	Incorrect intervention (not available in the UK)
Ogihara 2009 ⁸⁷	Incorrect study design. Not randomised to targets. Analysis investigates the association between achieved blood pressure and cardiovascular events, secondary analysis of a trial (CASE-J)
Ogihara 2010 ⁸⁸	Incorrect population. Population had previous cardiovascular disease
Shimamoto 2008 ¹⁰⁰	No comparator. Follow up of participants receiving open-label losartan for 5 years.
Solomon 2010 ¹⁰²	Less than minimum duration. Follow up for 24 weeks, less than 12 month minimum inclusion criteria
Wang 2005 ¹¹⁸	Systematic review, Incorrect comparison
Zanchetti 2009 ¹²⁴	Incorrect study design. Secondary analysis of multiple trials investigating the association between cardiovascular evetns and antihypertensive medication

Table 21: Studies excluded from the clinical review

Study (ID)	Exclusion reason
Anonymous 2017 ³	Incorrect study design
Arguedas 2010 ⁴	Literature review
Arima 2006 ⁷	Incorrect population
Aronow 2018 ⁸	Systematic review, references checked
Asayama 2017 ⁹	Incorrect comparison, Incorrect population
Bai 2015 ¹⁰	Incorrect interventions

Study (ID)	Exclusion reason
Baker 2000 ¹¹	Incorrect population
Bangalore 2013 ¹³	Not guideline condition
Bangalore 2014 ¹²	Not guideline condition
Bangalore 2016 ¹⁴	Editorial paper
Bangalore 2017 ¹⁵	Not guideline condition
Barry 2016 ¹⁶	Conference abstract
Bavishi 2017 ¹⁷	Systematic review, references checked
Beddhu 2018 ¹⁸	Subgroup analysis, not relevant
Beddhu 2018 ¹⁹	CKD subgroup of ACCORD and SPRINT
Benavente 2013 ²¹	Incorrect population
Berlowitz 2017 ²²	No relevant outcomes
Blackburn 2013 ²³	Study protocol
Blood Pressure Lowering Treatment Trialists 2008 ²⁴	Systematic review, references checked
Bohm 2018 ²⁵	Incorrect study population
Brubaker 2016 ²⁶	Literature review
Brunström 2018 ²⁷	No relevant outcomes
Burla 2014 ²⁸	Incorrect population
Cardio-sis study group 2008 ²⁹	Protocol
Chang 2017 ³⁰	No relevant outcomes
Chi 2018 ³²	Systematic review, references checked
Chrysant 2018 ³³	Incorrect study design - literature review
Coca 2008 ³⁵	Incorrect population. Population had coronary artery disease
Cushman 1998 ³⁶	No useable outcomes, Incorrect comparison
Daskalopoulou 2012 ³⁷	Guideline
Denardo 2010. ³⁸	Incorrect comparison, incorrect analysis. Secondary analysis of INVEST trial comparing participants on varapamil or atenolol based treatment.
Drawz 2017 ³⁹	No relevant outcomes
Estacio 2000 ⁴¹	Incorrect population
Estacio 2006 ⁴⁰	Incorrect population
Fagard 2007 ⁴²	Incorrect study design. Prognostic study predicting cardiovascular revents based on diastolic blood pressure
Fan 2017 ⁴³	Incorrect comparison
Feldstein 2010 ⁴⁴	Literature review
Fletcher 2016 ⁴⁵	Incorrect population
Garrison 2017 ⁴⁶	Systematic review, references checked
Gould 2013 ⁴⁷	Conference abstract
Gradman 2017 ⁴⁸	Literature review
Hassanein 2009 ⁴⁹	Less than minimum duration
Ho 2017 ⁵⁰	Protocol
Hosohata 2007 ⁵¹	No relevant outcomes
Howard 2008 ⁵²	Incorrect comparison (combination with statins)
Hyman 2009 ⁵³	Literature review

Study (ID)	Exclusion reason
Ichihara 2003 ⁵⁴	No relevant outcomes
Ishikawa 2008 ⁵⁵	Incorrect study design
Ismail-Beigi 2012 ⁵⁶	Incorrect comparison (combination with glycaemia targets)
Jafar 2015 ⁵⁷	Incorrect comparison
Janssen 2009 ⁵⁸	Incorrect comparison
JATOS study group 2005 ⁵⁹	Incorrect intervention(not available in the UK)
JATOS study group 2008 ⁶⁰	Incorrect intervention(not available in the UK)
Johnson 2018 ⁶¹	Wrong comparisons
Jonsson 2003 ⁶²	Published before cut off date
Karmali 2018 ⁶³	Systematic review, references checked
Kawano 2011 ⁶⁴	Incorrect intervention(not available in the UK)
Kjeldsen 2008 ⁶⁵	Incorrect population
Lachouri 2009 ⁶⁶	Incorrect study design
Lee 2018 ⁶⁷	Incorrect study population - diastolic hypotension subgroup of SPRINT trial
Liu 2017 ⁶⁸	Systematic review, references checked
Ma 2015 ⁶⁹	Incorrect population
Mancia 2016 ⁷¹	Incorrect study design
Mancia 2018 ⁷⁰	Systematic review, references checked
Manning 2014 ⁷²	Incorrect population
Mariampillai 2016 ⁷³	Meta-analysis, references checked
McBrien 2012 ⁷⁴	Systematic review, references checked
McCormick 2016 ⁷⁵	Letter to editor
McManus 2014 ⁷⁶	Incorrect comparison
Miskulin 2018 ⁷⁷	Incorrect population
Moon 2011 ⁷⁸	Abstract
Mosenkis 2004 ⁷⁹	Not article
Nielsen 2016 ⁸³	Incorrect population
Odden 2016 ⁸⁵	Incorrect population
Ogihara 2008 ⁸⁶	Incorrect study design, Incorrect population
Ogihara 2009 ⁸⁷	Incorrect study design. Not randomised to targets. Analysis investigates the association between achieved blood pressure and cardiovascular events, secondary analysis of a trial (CASE-J)
Ogihara 2010 ⁸⁸	Incorrect population
Papadopoulou 2018 ⁸⁹	Systematic review, references checked
Park 2017 ⁹⁰	Incorrect population
Pergola 2014 ⁹²	Incorrect population
Pool 2009 ⁹³	Incorrect comparison
Rakugi 2010 ⁹⁴	Incorrect intervention(not available in the UK)
Rosenberg 2016 ⁹⁶	Literature review
Saiz 2017 ⁹⁷	Incorrect comparison
Schrier 2002 ⁹⁸	Incorrect comparison
Schrier 2002 ⁹⁹	Incorrect comparison
Shimamoto 2008 ¹⁰⁰	No comparator. Follow up of participants

Study (ID)	Exclusion reason
	receiving open-label losartan for 5 years.
Soliman 2017 ¹⁰¹	SPRINT subgroup analysis (not relevant)
Solomon 2010 ¹⁰²	Less than minimum duration
Song 2016 ¹⁰³	Incorrect study design
Stewart 2015 ¹⁰⁴	Abstract
Still 2017 ¹⁰⁵	Subgroup analysis, not relevant
Supiano 2017 ¹⁰⁶	Literature review
Thomopoulos 2014 ¹⁰⁷	Incorrect population
Thomopoulos 2016 ¹⁰⁸	Systematic review, references checked
Thomopoulos 2016 ¹⁰⁹	Incorrect comparison
Tucker 2015 ¹¹⁰	Incorrect comparison
Turnbull 2003 ¹¹¹	Incorrect comparison
Turnbull 2005 ¹¹²	Systematic review, references checked
Ueki 2016 ¹¹³	Incorrect comparison
UK Prospective Diabetes Study Group 1998 ¹¹⁴	Before cut-off date
Verdecchia 2016 ¹¹⁵	Not available
Volpe 2011 ¹¹⁷	Not available
Wang 2005 ¹¹⁸	Systematic review, Incorrect comparison
Weber 2016 ¹¹⁹	Not available
Wei 2013 ¹²⁰	Incorrect population
Weiss 2017 ¹²¹	Systematic review, references checked
Williamson 2016 ¹²²	SPRINT subgroup analysis (not relevant)
Zanchetti 2009 ¹²⁴	Incorrect study design. Secondary analysis of multiple trials investigating the association between cardiovascular events and antihypertensive medication.
Zheng 2015 ¹²⁵	Incorrect study design

I.2 Excluded health economic studies

Table 22: Studies excluded from the health economic review

Reference	Reason for exclusion
Clarke 2005 ³⁴	This study was assessed as not applicable because the clinical trial the economic evaluation is based on is dated prior to the clinical protocol date cut-off of 2000.
Jonsson 2003 ⁶²	This study was assessed as not applicable because the clinical trial the economic evaluation is based on is dated prior to the clinical protocol date cut-off of 2000.
Penaloza-Ramos 2016 ⁹¹	This study was assessed as not applicable as it was a high risk population of people with a history of stroke.

Appendix J: Research recommendations

J.1 Targets

Research question: What is the optimum blood pressure target for people aged over 80 with treated primary hypertension?

Why this is important:

Stroke and heart failure are major causes of mortality and morbidity in older people. These conditions can result in loss of independence and a severe reduction in quality of life. A major modifiable risk factor for both stroke and heart failure is hypertension, and evidence exists to show that drug treatment can reduce rates of death from stroke and heart failure in selected older populations. However, considerable observational data confirms a U-shaped relationship between blood pressure and mortality in people aged 80 and over.

Antihypertensive medication has potential side effects to which older people are particularly prone. There is a need to find the optimal balance between lowering blood pressure with medication and the frequency with which adverse reaction to medication occurs. How intensive should blood pressure treatment in the older person be, and how should treatment targets be modified in those who are frail, have cognitive impairment or who have a low diastolic blood pressure (BP)?

Criteria for selecting high-priority research recommendations:

PICO question	<p>Population: People aged 80 and over diagnosed with hypertension (including subgroups: presence or absence of frailty, cognitive impairment, or low diastolic BP at baseline).</p> <p>Intervention(s): Treatment of hypertension to a target blood pressure of below 140/90 as measured in the UK general practice clinical setting or a home or ambulatory blood pressure target of below 135/85.</p> <p>Comparison: Treatment of hypertension to a target blood pressure of below 150/90 as measured in the UK general practice clinical setting or a home or ambulatory blood pressure target of below 145/85.</p> <p>Outcome(s): All-cause mortality, stroke (ischaemic or haemorrhagic), myocardial infarction, hospitalisation due to angina, heart failure, acute kidney injury or falls, discontinuation or dose reduction of antihypertensive agents due to side-effects and comparison of health related quality of life.</p>
Importance to patients or the population	Evidence indicates that in selected older people treating to a target blood pressure of below 150/90 reduces the rate of all-cause mortality, stroke and heart failure with an acceptable rate of adverse reaction to medication. A recent study suggested that there might be additional benefit to treating to a lower target. However, the positive results seen in selected populations may not be replicated when the same treatments are applied to those who are at higher risk of adverse effects of medication.
Relevance to NICE guidance	Evidence on treating to a lower blood pressure target in people aged over 80 would inform future updates of this guidance. Current guidance recommends a lower blood pressure target for people aged under 80 of below 140/90, as evidence is lacking for more intensive treatment in those aged 80 and over, especially. Current guidance recommends a target of below 150/90 in those aged 80 and over.
Relevance to the NHS	There is the potential to reduce mortality and morbidity in people aged 80 and over. This could in turn results in cost savings.
National priorities	This is consistent with the National Service Framework for Older People
Current evidence base	The only randomised controlled clinical trial of treatment targets for hypertension in older people was comparing a target of below 150 mmHg to no treatment, which was included in the previous guideline iteration.

	Other studies comparing more intensive targets to less intensive targets were included within this review, but none of these looked specifically at people aged over 80. Further research is therefore required to determine if the benefits of intensive treatment outweigh the risks in UK general practice.
Equality	The frail elderly are more at risk of adverse reaction to antihypertensive agents and therefore need special consideration
Study design	Randomised clinical trial (RCT)
Feasibility	Feasibility issues relate to funding and recruitment. The study would be based in UK primary care and may utilise the existing primary care research networks. The previous study recruited 2,510 people aged 75 and over. A comparative cohort design may help overcome some of the recruitment issues in this population, however it may be less informative to future updates of the guideline and hasn't been recommended for that reason.
Other comments	None
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.